THE TOTAL SYNTHESIS OF MUAMVATIN

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By

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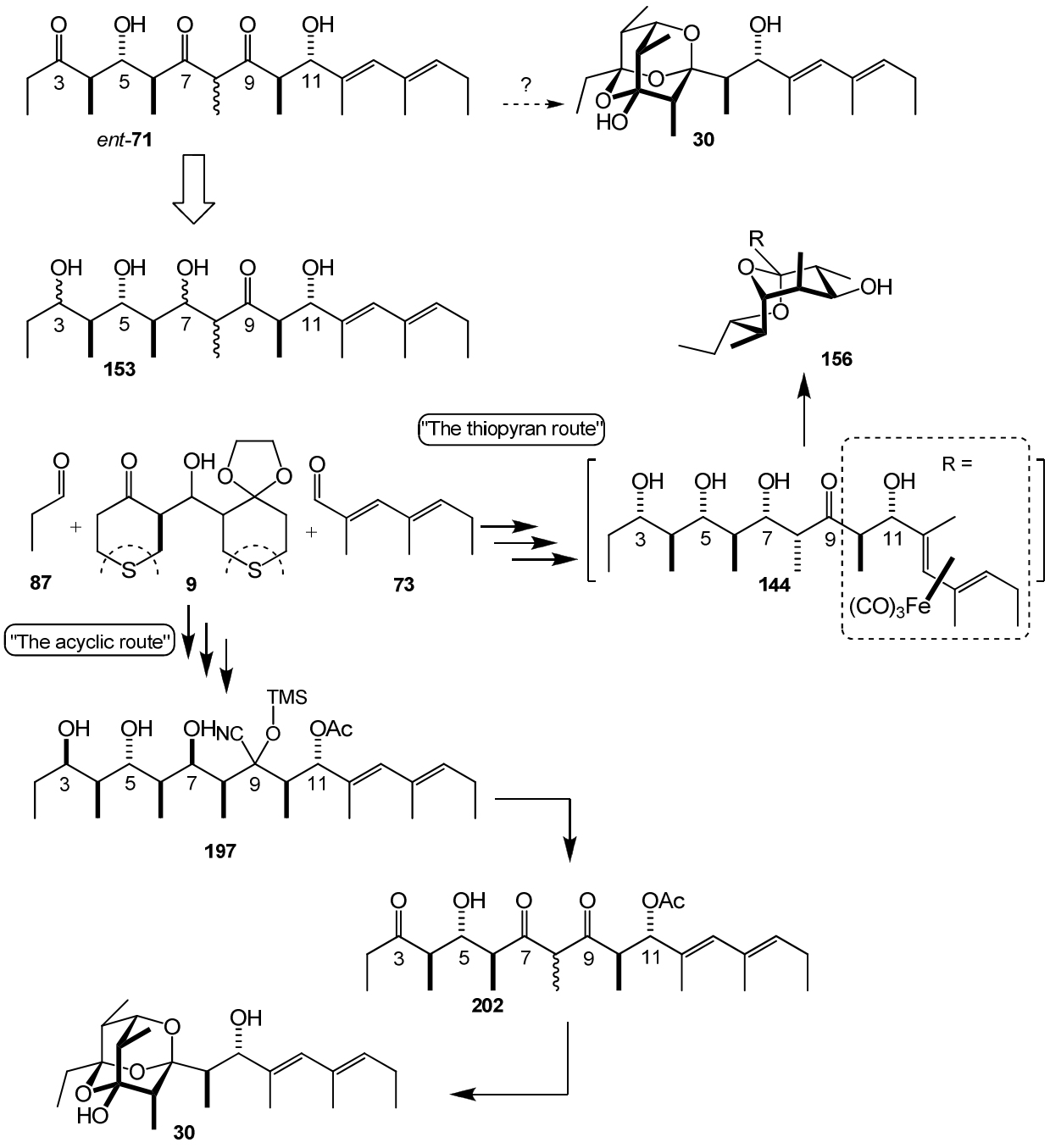
ABSTRACT

Muamvatin (**30**) is a polypropionate natural product isolated from *Siphonaria normalis* by Ireland et al. in 1986. Muamvatin (**30**) is made from eight propionate units and contains an extraordinary trioxaadamantane ring system. This ring system exists in only one other naturally occurring polypropionate known as caloundrin B. Regarding the rare muamvatin trioxaadamantane ring system, it was hypothesized this ring system may not be formed via an enzymatic process and the actual natural product could be the linear precursor *ent*-**71** which cyclizes to muamvatin (**30**) during isolation. The first total synthesis of muamvatin (**30**) by Paterson et al. confirmed its absolute and relative configuration, but the ambiguity regarding the origin of the trioxaadamantane ring system in this molecule remains unresolved.

This work describes two approaches to make the linear precursor *ent*-**71** from triol ketone **153**. The carbon skeleton of muamvatin was synthesized through two iterative diastereoselective aldol reactions. In the first approach, "the thiopyran route", the diene moiety of aldehyde **73** required protection to avoid reduction during desulfurization. Although use of the tircarbonyliron complex was successful, the trihydroxy ketone revealed upon desulfurization was unstable and spontaneously cyclized to bicyclic acetal **156**. Molecular mechanics revealed that the relative configurations embedded in C3, C7, and C8 dramatically effected the stability of the corresponding bicyclic acetal. With that lesson learned, the fully assembled linear precursor **197** was made in our second approach "the acyclic route". The oxidation state of the backbone oxygens were manipulated via an unusual chemoselective double Swern oxidation. Finally, revealing the sensitive 5-hydroxy-3,7,9-trione functionality formed the precursor **202**. Efficient

cyclization of precursor **202** and removal of the protecting group at C11-OH produced the desired natural product **30**. The cyclization conditions tested on the linear precursor **202**, suggested that although the cyclization to the trioxaadamantane is strongly favored thermodynamically, the process is very slow and unlikely to occur during the isolation process. Thus, formation of the trioxaadamantane ring system could be an enzyme-mediated process as was concluded for caloundrin B.


ent-71
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153
156
87
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73
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R =
(CO)3Fe
"The thiopyran route"
"The acyclic route"
197
202
30

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LIST OF ABBREVIATIONS

$[\alpha]_D$	specific rotation (expressed without units; the actual units, (deg·mL)/(g·dm), are implied)
Ac	acetyl
ap	apparent (spectral)
aq	aqueous
Ar	aryl
9-BBN	9-borabicyclo[3.3.1]nonyl
Bn	benzyl
bp	boiling point
br	broad (spectral)
Bu	butyl
^{t}Bu	*tert*-butyl
°C	degrees Celsius
calcd	calculated
cat.	catalytic (abbreviation used with period)
CI	chemical ionization
CIF	crystallographic information file
cm	centimeter(s)
COSY	correlation spectroscopy
c-Hex	cyclohexyl
Chx	cyclohexyl
δ	chemical shift in parts per million
d	doublet (spectral)

DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEPT	distortionless enhancement by polarization transfer
DIBAL-H	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMPU	1,3-dimethyltetrahydropyrimidin-2-one
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
DRIFT	diffuse reflectance infrared fourier transform spectroscopy
ee	enantiomeric excess
EI	electron impact
ent	enantiomer of
epi	epimer of
equiv	equivalent
er	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
FCC	flash column chromatography
FTIR	fourier transform infrared
h	hour(s)
HMBC	heteronuclear multiple bond correlation

HMDS	hexamethyldisilazane, bis(trimethylsilyl)amide
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
Hz	Hertz
IBX	2-iodoxybenzoic acid
IR	infrared
J	coupling constant (in NMR spectroscopy)
KHMDS	potassium bis(trimethylsilyl)amide
KR	kinetic resolution
LDA	lithium diisopropylamide
lit.	literature value
LRMS	low resolution mass spectrometry
M	molar (moles per liter)
M^+	parent molecular ion
m	multiplet (spectral)
Me	methyl
MHz	megahertz
min	minute(s)
MKE	mutual kinetic enantioselection
mol	mole(s)
MOM	methoxymethyl
mp	melting point

MS	mass spectrometry
Ms	methanesulfonyl or mesyl
MW	molecular weight
m/z	mass-to-charge ratio
ν	frequency
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
ORTEP	Oak Ridge thermal ellipsoid plot
PCC	pyridinium chlorochromate
Pd/C	palladium on charcoal
PDC	pyridinium dichromate
PG	protecting group
Ph	phenyl
PKS	polyketide synthetase
PMA	phosphomolybdic acid
PMB	*p*-methoxybenzyl or *p*-methoxyphenylmethyl
ppm	part(s) per million
PPTS	pyridinium *para*-toluenesulfonate
^{i}Pr	*iso*-propyl
Pr	propyl
PTLC	preparative thin-layer chromatography
PTSA	*p*-toluenesulfonic acid

Py	pyridine
q	quartet (spectral)
quant	quantitative
rac	a prefix to denote racemic
Raney Ni	Raney® nickel
Ref.	reference
Refs.	references
R_f	retention factor (in chromatography)
rel	relative
rt	room temperature
s	singlet (spectral); second(s)
SAM	*S*-adenosyl methionine
t	triplet (spectral)
t	time
TBAF	tetrabutylammonium fluoride
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMS	trimethylsilyl
TOF	time-of-flight (in mass spectrometry)

Ts	tosyl (*para*-toluenesulfonyl [*p*-CH_3-C_6H_4-SO_2])
v/v	volume per unit volume (volume-to-volume ratio)
wt	weight

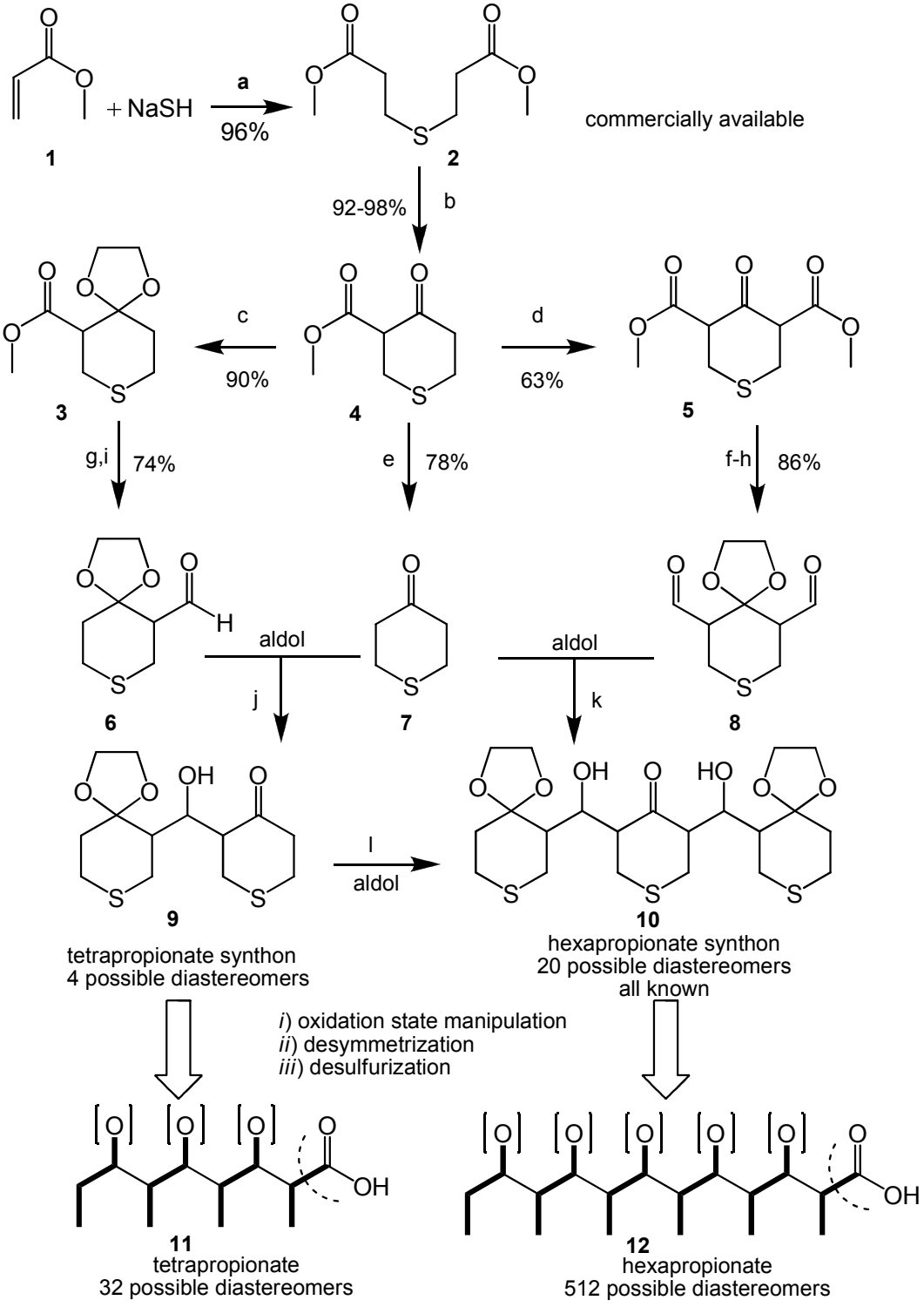
1. INTRODUCTION

1.1 The thiopyran route to polypropionates

The thiopyran route to polypropionates has been one of the research themes in the Ward group for several years.[1] This strategy featured by simple, scalable, and cost-efficient procedures for preparation starting materials.[2,3] Easy desulfurization of the final products and flexible chemistry make the thiopyran templates quite popular. During the last decade, the essential elements of this strategy were explored extensively in the Ward group (**Scheme 1.1**). Different approaches such as the iterative aldol reaction of tetrahydro-4*H*-thiopyran-4-one **7** with carboxaldehyde **6**[4,5] or a simultaneous aldol reaction of dialdehyde **8** with tetrahydro-4H-thiopyran-4-one **7** were developed.[6] All these efforts provided rapid access to tetra and hexapropionate synthons.

The difficulty in selectively accessing hexapropionate **12** is revealed when considering the 512 possible diastereomers (**Scheme 1.1**). This number decreased to 20 diastereomers in **10** by disconnecting the carboxyl group and adjusting oxidation states of oxygen atoms. Previous results demonstrated that all 20 possible diastereomers could be obtained through iterative two-directional aldol reactions or simultaneous aldol reaction of tetrahydro-4*H*-thiopyran-4-one **7** and dialdehyde **8** (**Scheme 1.1**).[4,6,7] Controlling the stereoselectivity of these aldol couplings is an ongoing objective in the Ward group. To date, the thiopyran route has been used successfully in total syntheses of several polypropionate natural products such as serricornin,[8] membrenone B[9], baconipyrone C[10] (**44**), baconipyrone A[10] (**43**), siphonarin B[10] (**28**) and *ent*-caloundrin B.[11]

Scheme 1.1 The thiopyran route to polypropionates



a) $NaHCO_3$; b) Na, MeOH; c) $(HOCH2)_2$, PTSA (cat.); d) LDA, $ClCO_2Me$; e) 10% H_2SO_4; f) $(TMSOCH_2)_2$, TMSOTf; g) $LiAlH_4$; h) $(COCl)_2$, DMSO, Et_3N; i) IBX; j) refs. 12, 13 k) ref. 6 l) refs. 4, 5.

1.1.1 Preparation of the tetrapropionate synthons 9

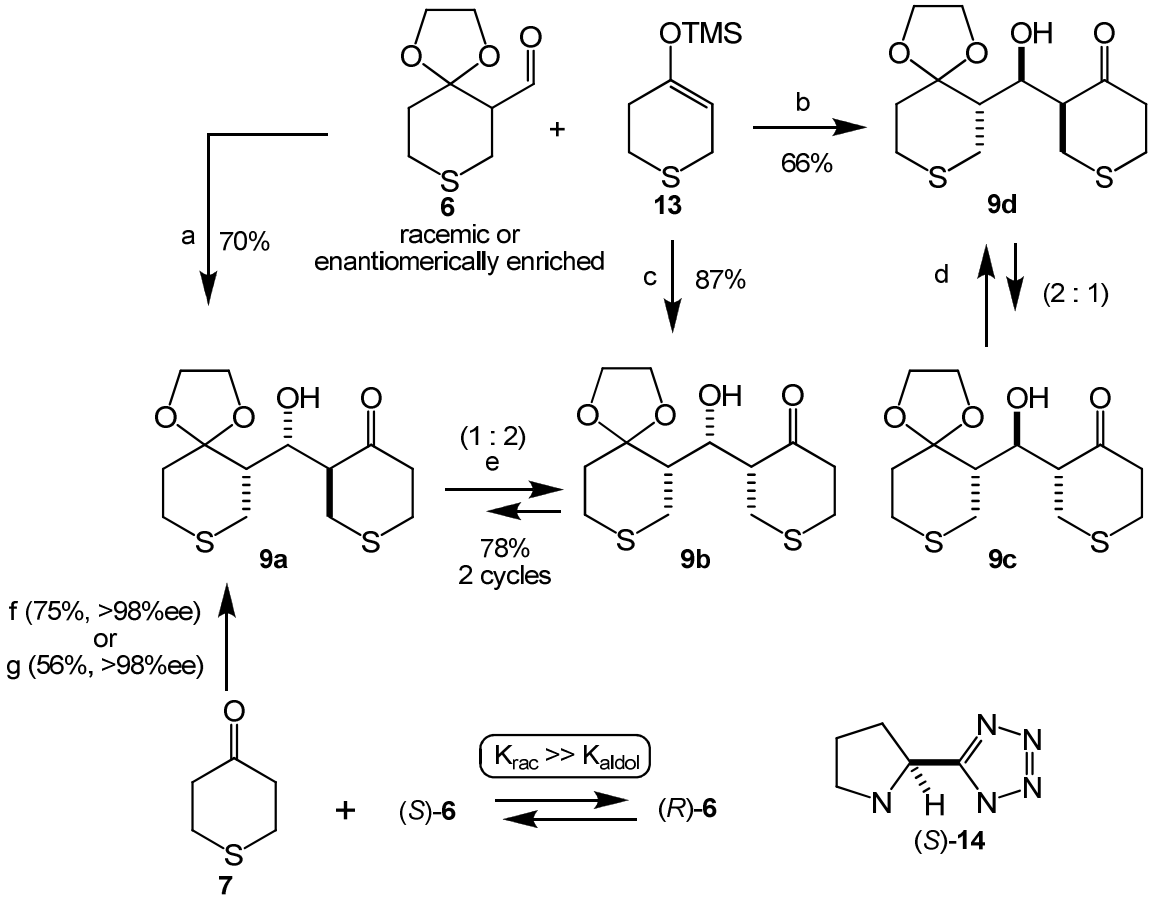
The preliminary building blocks in the thiopyran route to polypropionates are the four tetrapropionate synthons **9**. The aldol reaction between easily accessible silyl enol ether **13**[2] and aldehyde **6** can form four possible diastereomers **9** (**Scheme 1.2**). Three out of four possible diastereomer can be produced with high selectivity by using different mediators such as $MgBr_2 \cdot OEt_2$, MeLi and $TiCl_4$.[12] The least accessible diastereomer **9c**, was obtained via imidazole mediated isomerization of **9d**.[13]

Synthesis of enantiomerically pure polypropionate natural products typically requires starting from enantiomerically enriched building blocks. In the thiopyran route to polypropionates, each of the four tetrapropionate synthons (**9a**-**9d**) can be prepared in enantiopure form by following the same procedures but starting from enantiopure aldehyde **6** (**Scheme 1.2**).[14] Alternatively, recent investigations established a new method for enantioselective preparation of tetrapropionate synthons **9a** via enantiotopic group selective direct aldol reaction of racemic aldehyde **6** with ketone **7**, mediated by (*S*)-proline as the desired organocatalyst.[15,16]

Although this reaction provided **9a** with high enantioselectivity (>98%ee), the yield still needed to be improved. Meticulous optimization showed that a large excess of ketone **7** (i.e. 8 equiv) was needed to obtain a yield 56%. Applying the tetrazole catalyst **14**, which has higher solubility, and increasing the concentration considerably reduced the amount of required ketone (2 equiv *vs*. 9 equiv) and improved the yield to 75% on multi-gram scale without need for chromatography while maintain high enantioselectivity (>98%ee).[3] Isomerization of enantiomerically enriched aldol adduct **9a** via methods mentioned previously, provides **9b** the thermodynamically more stable diastereomer without loss of enantioenrichment. Thus two out of the four diastereomers of the aldol

adduct **9** can be efficiently prepared in enantiopure form from racemic and achiral reactants (**Scheme 1.2**).

Scheme 1.2 Preparation of the first aldol adducts



a) MeLi; b) $MgBr_2 \cdot Et_2O$; c) $TiCl_4$; d) Imidazole, $CHCl_3$; e) SiO_2, Et_3N; f) **14** (20 mol%) **14**, wet DMSO; g) (*S*)-proline, wet DMSO.

1.1.2 Preparation of hexapropionate synthons 10

An aldol reaction of any of the four tetrapropionate synthons **9** with aldehyde **6** results in formation of hexapropionate synthons **10** (**Scheme 1.1**). As mentioned

previously, all twenty possible diastereomeric forms of hexapropionates **10** are known and methodology studies established access to all possible diastereomers.[4,5,7,13,17]

In order to understand the diastereoselectivity in the aldol reaction of ketones **9a-d** and aldehyde **6**, some terms should be identified. Seebach and Prelog proposed the terms *like* and *unlike* to differentiate the reactions of two chiral reactants,[18] in this case ketones **9a-d** and aldehyde **6**. The term *like* is used when the fiducial stereogenic centers of the aldehyde and the ketone reactants have the same absolute configuration and the term *unlike* is used when the fiducial stereogenic centers of the reactants have different absolute configurations.

At least three stereochemical control elements dictate the diastereoselectivity in an aldol reaction between chiral reactants. These are the enolate and aldehyde diastereoface selectivity, and the aldol relative topicity. When these three stereochemical controlling elements reinforce each other the aldol reaction is highly diastereoselective and is called a "matched"[19,20] reaction. On the other, hand, if they do not reinforce each other, the reaction is called "mismatched"[19,20] and will proceed with diminished diastereoselectivity. Another important concept for reactions of chiral reactants in racemic form is mutual kinetic enantioselection (MKE).[21] This term refers to the relative facility (rate constants) of the *like* versus *unlike* reactions.

Previous results of aldol reactions between ketone **9a-d** and aldehyde **6** were based on Ti(IV) enolates formed by reaction of the ketones with $TiCl_4$ or $Ti(O^iPr)Cl_3$ and an amine base (**Figure 1.1**).[4] Analysis of the product distributions of these reactions illustrates both the diastereoselectivities and the relative rates of the *like* and *unlike*

reactions. It was also observed that the condition of the ß-hydroxyl group (protected or unprotected) strongly influences diastereoselectivity in the aldol reactions.

Each reaction (i.e., **15** or **17** with racemic aldehyde **6**) can form eight possible diastereomers, four each from the *like* and *unlike* combinations of reactant enantiomers. In this investigation, *like* refers to the same absolute configurations at C3 of the ketone and C3" of the aldehyde, while *unlike* refers to the opposite absolute configurations at C3 of the ketone and C3" of the aldehyde. Ward et al. demonstrated that the reactions of ß-hydroxy ketones occur with high diastereoselectivity and high MKE, while the reactions of the related ß-alkoxy ketones occur with high diastereoselectivity but low MKE. The reactions that occurred with high MKE using racemic reactants proceed with the expected kinetic resolution using enantiomerically enriched ketone and racemic aldehyde thereby, allowing access to enantiomerically enriched hexapropionate synthons.

The aldol reaction of the enolate **15** (formed directly from ß-hydroxy ketones **9**) with racemic aldehyde **6** selectively formed one of the eight possible diastereomers. Analysis of the product from this reaction shows that the stereoselectivity of the *unlike* combination of the starting materials reinforce each other and produce one product specifically. Because no product from the *like* combination of starting materials was observed, the reaction must have occurred with a high level of MKE (**Figure 1.1, section *i***). Consequently, for each of the four diastereomers **15** the reactions were repeated using enantiomerically enriched ketones and racemic aldehyde **6**. These reactions proceeded with kinetic resolution to form enantiomerically enriched aldol adducts **16**.

In contrast the aldol reaction of the related ß-alkoxy enolate **17** with the same aldehyde **6** under the similar conditions proceeded with completely different

diastereoselectivity (**Figure 1.1, section *ii***). Analysis of the reactions for each diastereomer of **17** showed approximately 1:1 ratio of two aldol products, one from each possible combinations (*like* and *unlike*). Analysis of the results for each diastereomer of **17** showed one of the stereocontrol elements (aldol relative topicity) was not biased. Consequently, both *like* and *unlike* combinations of aldol partners (enolates **17** and aldehyde **6**) were matched and each reaction selectively gave one of the four possible products. Because the *like* and *unlike* occurred with a similar facility, (low MKE) two products were produced in near equal amounts.

In conclusion, having access to enantiomerically enriched bis-aldol adducts from the ß-alkoxy ketone series requires enantiomerically enriched aldehyde *and* ketone while the enantiomerically enriched bis-aldol adducts from the ß-hydroxy ketone series require only one of the partners to be enantiomerically enriched (the reactions proceed with KR).

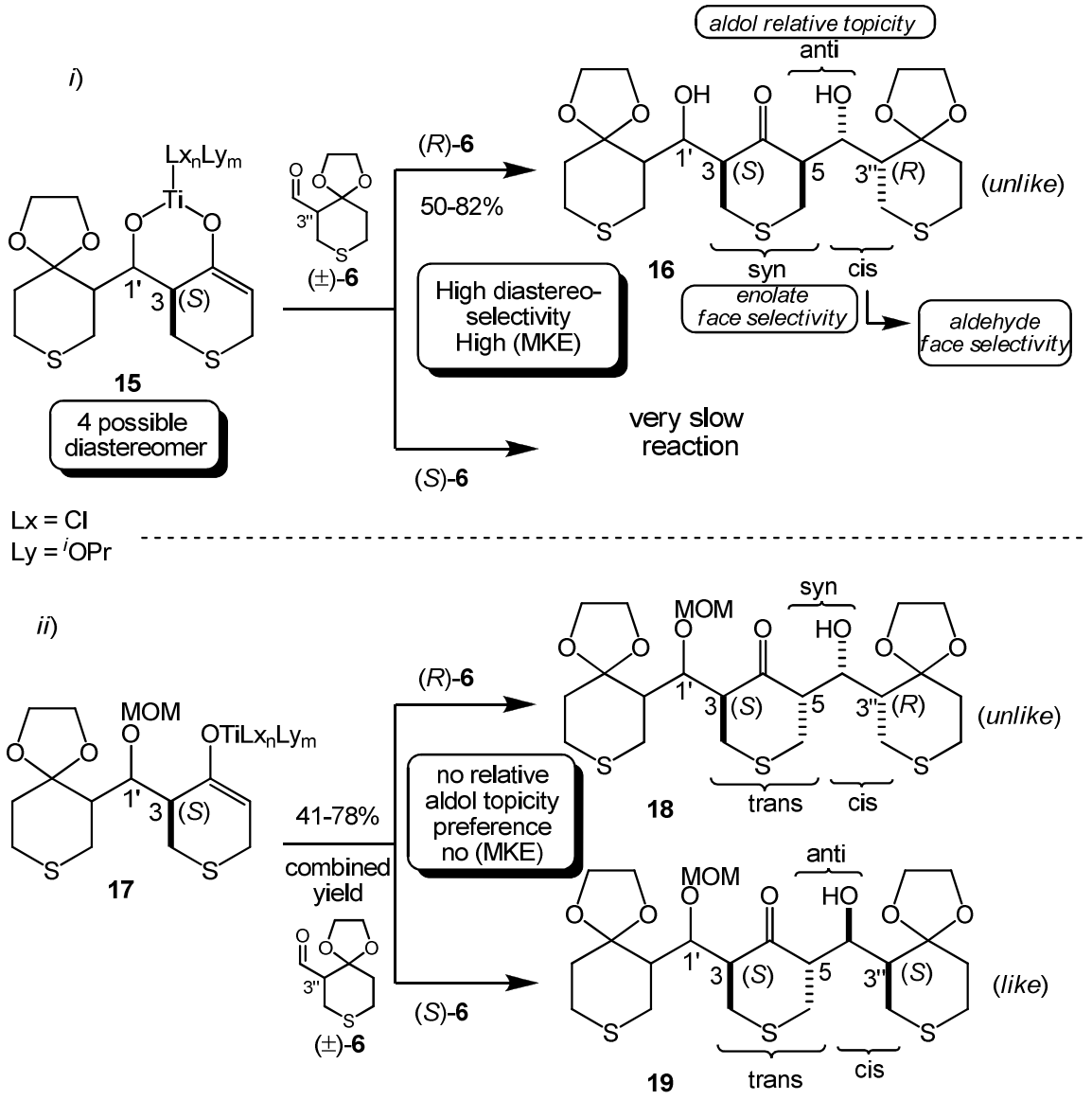


Figure 1.1 Stereoselectivity in the synthesis of hexapropionate synthons

My contribution to this area of research concerned the development of aldol reactions of the protected ß-hydroxy enolates **20** with racemic aldehyde **6** that proceed via kinetic resolution with tunable enantioselectivity.[5] In this project applying different enolates such as boron and titanium "ate" complex strongly enhanced the aldol relative topicity (the stereocontrol element that was not biased in the previous approach to

hexapropionate synthons). Hence, enantiomerically enriched aldol adducts (**21** and **22**) were formed selectively by starting from enantiomerically enriched ß-hydroxy enolates **20** and racemic aldehyde (±)-**6** via kinetic resolution (**Figure 1.2**). Having access to enantiomerically enriched hexapropionates **10** or tetrapropionates **9** provided an avenue for applying these templates in the total synthesis of polypropionates.

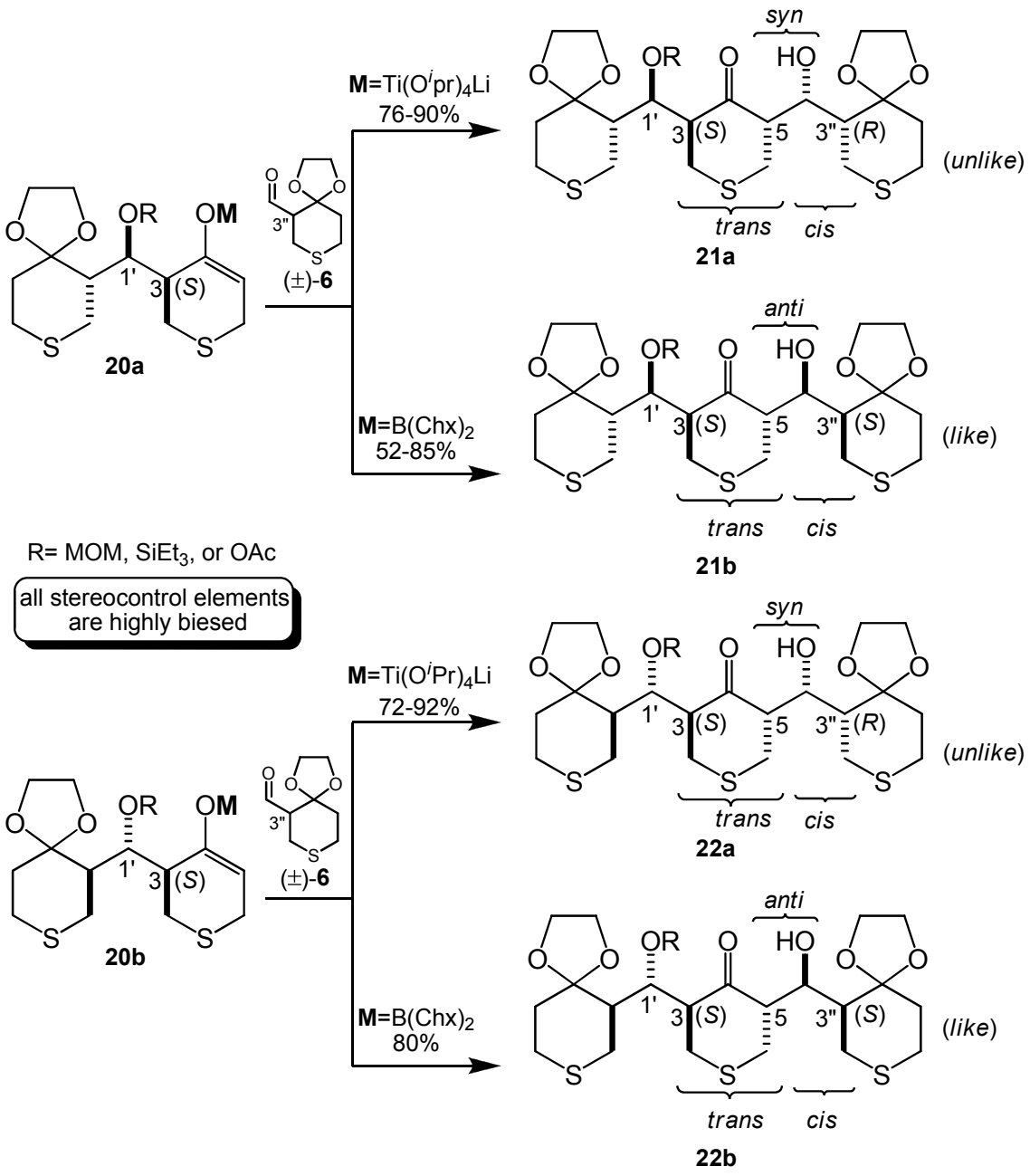


Figure 1.2 Tunable enantioselectivity in the hexapropionate synthesis

1.2 Introduction to siphonariid mollusks and their polypropionates

Siphonariid mollusks (genus *Siphonaria*) are small air breathing sea snails known as the most ancient pulmonates. These species can be found either in tropical or

temperate coast lines at intertidal zones around the globe.[22] Regarding their unique respiratory system (transformed lung sacs instead of gills), they may represent an evolutionary link between the marine and land mollusks. Although these mollusks feed on algae at low tides, there is no evidence to support their assimilation of algal metabolites from their food. Instead, it has been shown that their polypropionate-based metabolites originate from *de novo* biosynthesis.[23]

Although, siphonariid mollusks are primitive in evolutionary terms, they are extraordinary architects of a variety of polypropionate natural products and regardless of their geographical locations, they produce similar polypropionate metabolites.[24] These polypropionates have been categorized into two classes.[22] Class **I** includes acyclic systems (e.g., siphonarienone (**23**), and isosiphonarienolone (**25**)), and compounds with 2-pyrone and furanone ring systems (e.g., diemenensin A (**24**), and deoxysiphonarienfuranone (**26**)). An (*S*) absolute configuration at all methyl bearing stereogenic centers in the linear chain is characteristic of this class. While Class **I** represents structurally mundane polypropionates, Class **II** comprises much more complex and heavily oxygenated networks that commonly are cyclized to either γ-pyrone and/or spiroacetal ring systems (e.g., siphonarin A (**27**) and B (**28**), caloudrin B (**29**), and muamvatin (**30**)) (**Figure 1.3**).

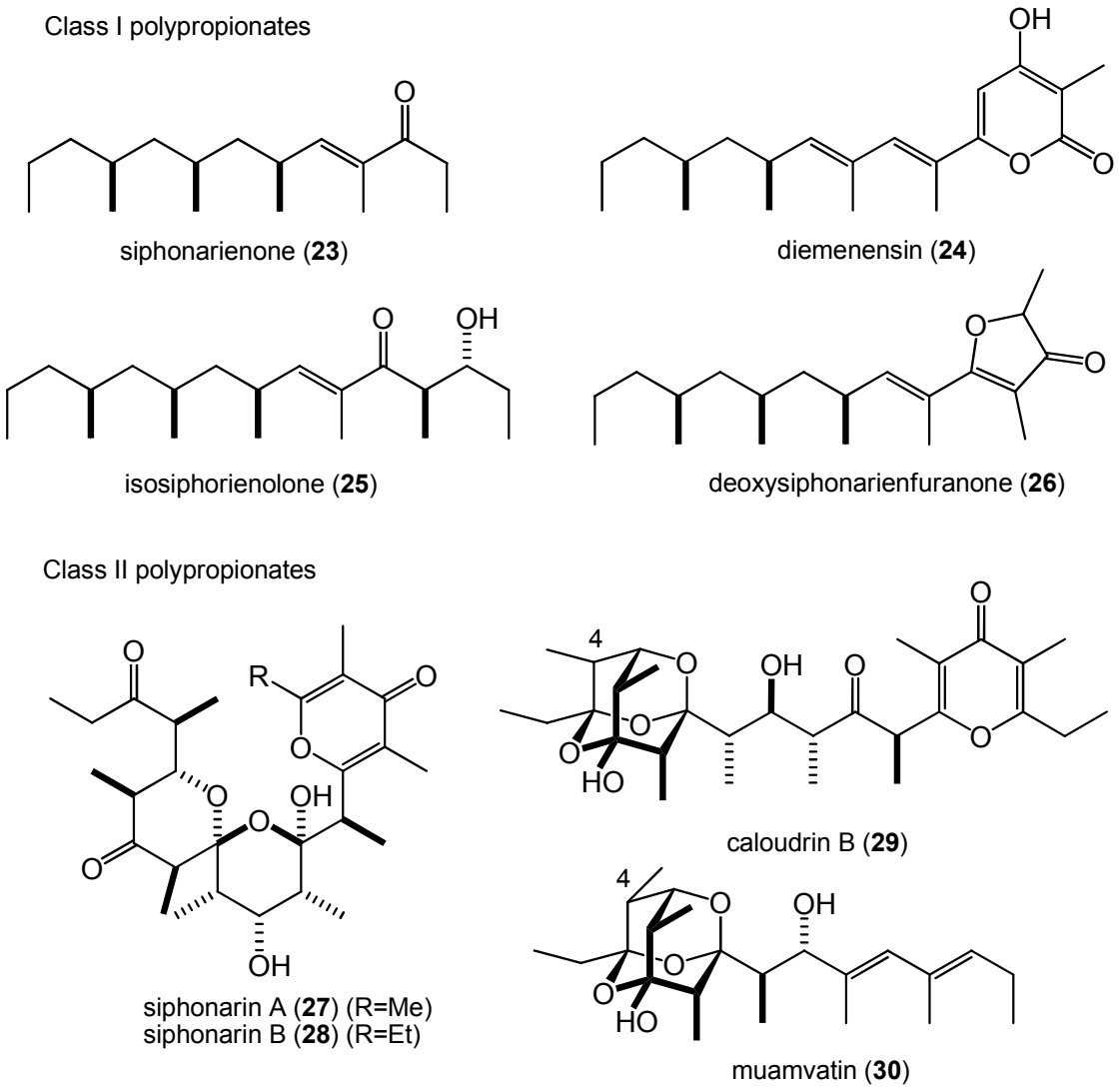


Figure 1.3 Examples of polypropionates from siphonariid pulmonates

Class **II** siphonariid polypropionates show much more complexity in comparison to Class **I**. This complexity can be attributed to the polyoxygenated backbone of the molecule as well as various cyclization modes that create different ring systems in this class. For instance, formation of trioxaadamantanes from 3-hydroxy-1,5,7- triones, γ-pyrones from 1,3,5-triones, and tetrahydro-2-hydroxy pyrones from 5-hydroxy-1,3-diones. It is also reasonable to consider that the same polyoxygenated backbone can be cyclized into various architectures. Such considerations suggest that seemingly different

polypropionates might originate from a common linear or thermodynamically unstable precursor.[10,11,23]

Extensive experimentation has shown that polyketides are synthesized in nature by multifunctional enzymes called polyketide synthases (PKSs).[25] Such enzymes are capable of condensing a malonic acid derivative with an activated thioester and simultaneous decarboxylation of the malonic acid. The product ß-ketoester can be further modified (e.g., keto-reduction, dehydration, enoyl-reduction) prior to the next cycle. In a different approach, methylation of a preformed polyacetate chain by S-adenosyl methionine is the second pathway known in polpropionate synthesis (**Figure 1.4**).[26]

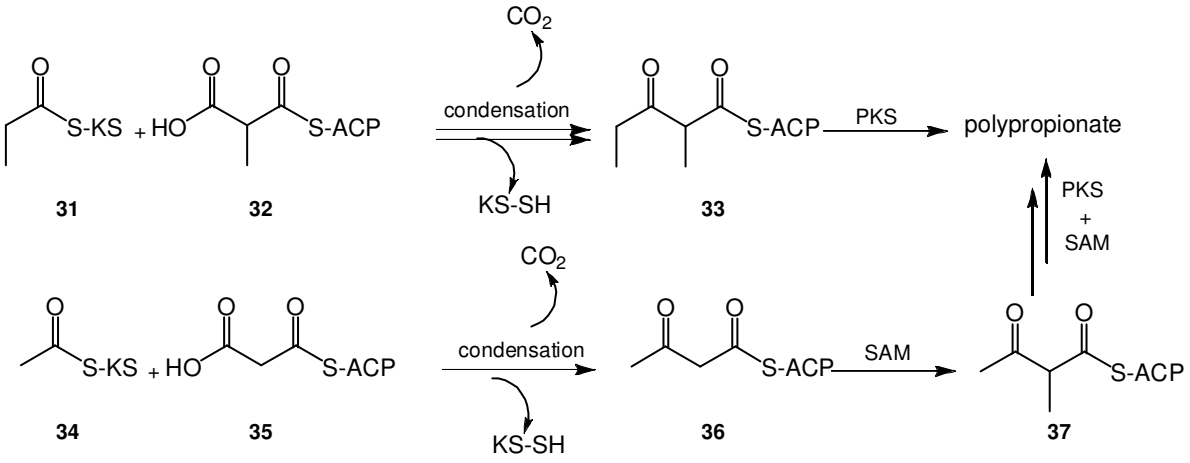


Figure 1.4 Biosynthesis pathways

One of the first studies in biosynthesis of polypropionates from siphonariid mollusks was done by Garson et al.[27] Injection of sodium [1-^{14}C] propionate to the foot muscle of *S. denticulate* resulted in incorporation of ^{14}C propionate units in the harvested denticulatin A (**39**) (**Figure 1.5**) demonstrating *de novo* biosynthesis.[27]

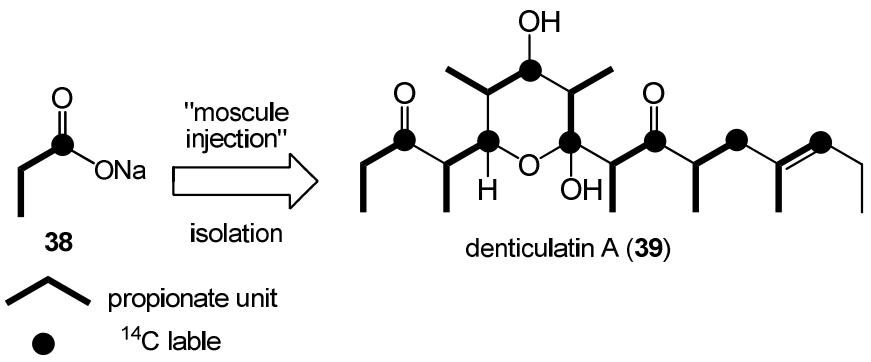


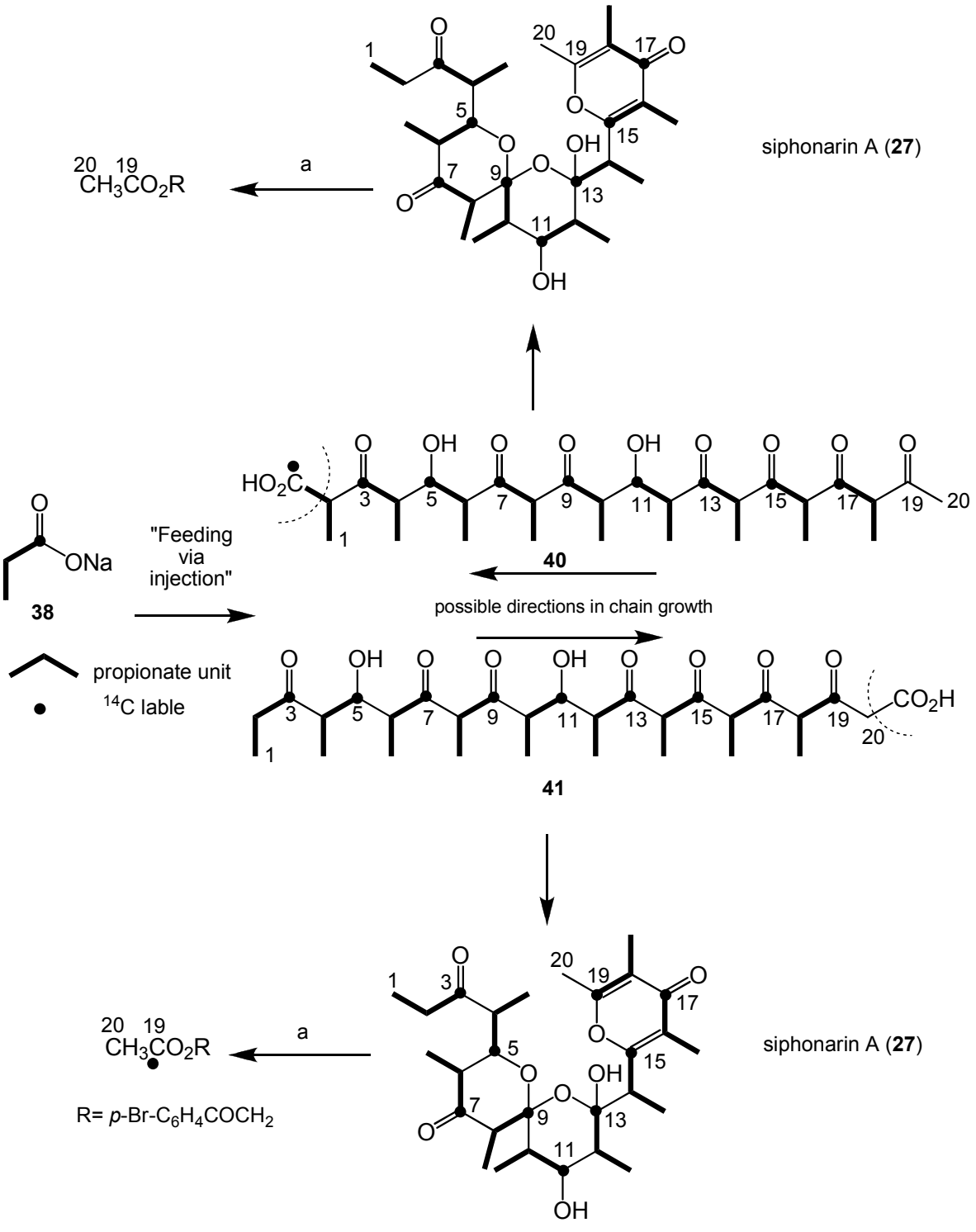
Figure 1.5 Biosynthetic studies on denticulatin A (**39**)

Decarboxylation of the terminal propionate unit after condensation results in ambiguity with respect to the direction of polypropionate chain extension. Garson et al. were able to answer this question by using the method described previously.[27] Siphonarin A (**27**), isolated from *S. zelandica*, consists of nine propionate units and one acetate unit. Feeding sodium [1-^{14}C] propionate to *S. zelandica* via injection in the foot pad showed incorporation of ^{14}C in the biosynthesized siphonarin A (**27**) chain (**Scheme 1.3**). Analysis of the acetate containing degradation product from the natural product did not show any incorporation of ^{14}C. This result indicated that the chain growth is starting from C20 to C1 direction and not the other way (**Scheme 1.3**).

Although polypropionate biosynthetic pathways have been extensively studied, it is still not clearly defined whether the cyclized products isolated are formed via enzymatic or non-enzymatic processes. The isolation of polypropionates from siphonariid mollusks usually involves multiple extraction and chromatography steps. Of the many siphonariid polypropionates known, it is not uncommon to find a hemiacetal, a pyrone ring system, or both structural motifs present in the natural product. Unraveling such ring systems by hypothetical ring-chain tautomerism (after hydration in case of pyrone) leads to heavily oxygenated linear precursors with several stereogenic centers.[28,29] Considering

such a linear precursor as the "starting material" and exposing it to the isolation conditions may result in spontaneous, thermodynamically controlled cyclization to one or more products. As the result, several different polypropionate "natural products" may form from a similar precursor. For instance, hypothetical ring opening/rearranging of four polypropionates from *S. zelandica*: siphonarin B (**28**), caloundrin B (**29**), baconipyrone A (**43**), and baconipyrone C (**44**) results in the same linear precursor (**42**). Recently Beye and Ward successfully synthesized the putative precursor **42** as a kinetically stable compound.[10] Interestingly, siphonarin B (**28**), baconipyrone A (**43**), and baconipyrone C (**44**) were obtained from **42** under different reaction conditions. Such observations suggested that the isolated natural products: siphonarin B (**28**), baconipyrone A (**43**), baconipyrone C (**44**) could be artifacts of isolation rather than the result of an enzymatic process (**Figure 1.6**).[10,27,30] By contrast, caloundrin B (**29**) could not be detected in various attempts to isomerize **42**. Beccerril-Jiménez and Ward prepared caloundrin B (**29**) by a different route and showed that it was much less thermodynamically stable than siphonarin B (**28**) and **42**.[11] Consequently, caloundrin B (**29**) can not be an artifact formed from **42** or siphonarin B (**28**) but might be the actual natural product from which **28**, **43**, and **44** can be derived.

Scheme 1.3 Biosynthetic studies on siphonarin A (**27**)



a) O_3,CH_2Cl_2, -78ºC; b) H_2O, then *p*-Br-$C_6H_4COCH_2Br$.

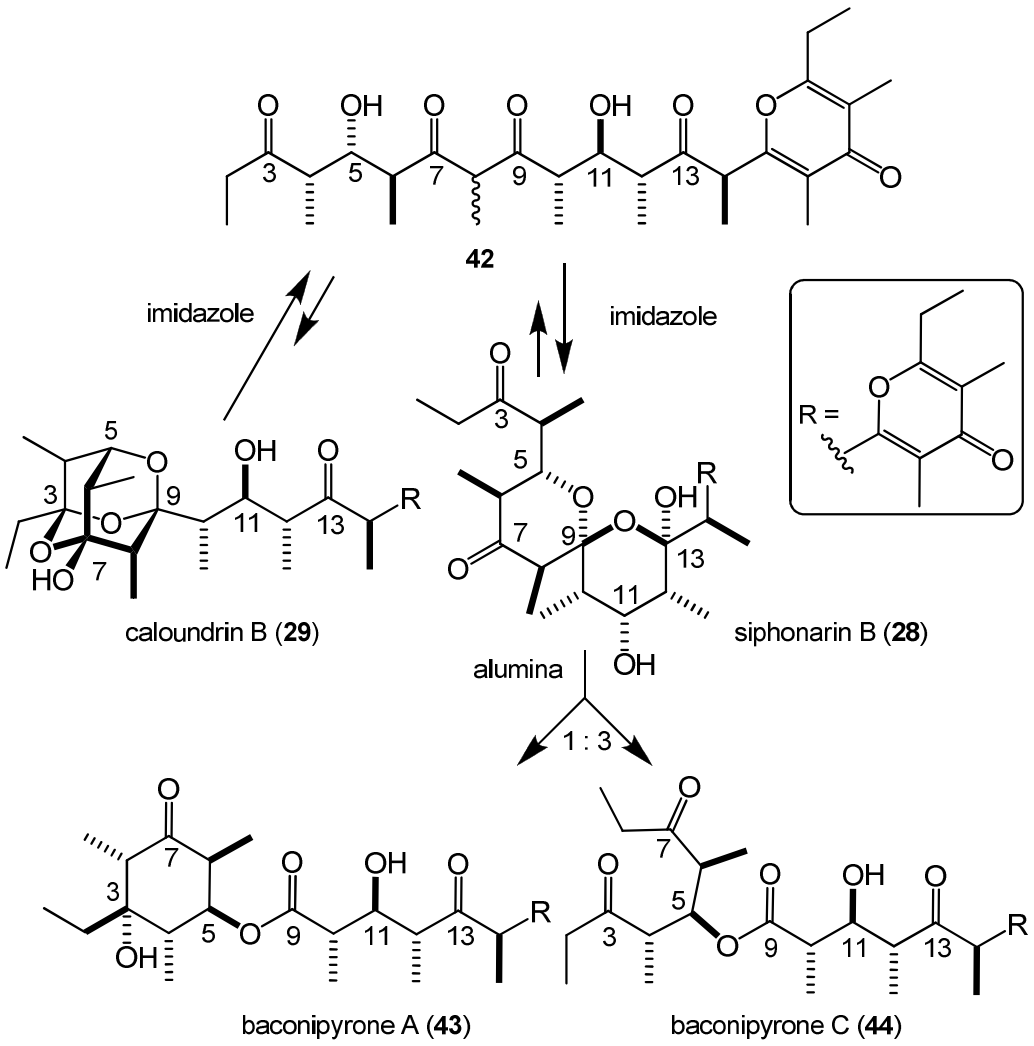


Figure 1.6 Siphonariid decapropionates rearrangement pathways

1.3 Isolation and structure determination of muamvatin

In 1986, Ireland et al. isolated an extraordinary polypropionate metabolite from *Siphonaria normalis*. These mollusks were collected intertidally from a region called Muamvatu in Fiji. The carbon tetrachloride extract of *S. normalis* contained the major portion of an unusual polypropionate. Extensive chromatography of this extract yielded 65.2 mg of a polypropionate natural product named muamvatin. Unlike other polypropionates isolated from pulmonate mollusks, muamvatin showed highly unusual

structural features such as a trioxaadamantane ring system as well as an unsaturated diene moiety.[30] The chemical ionization mass spectrum (CIMS) of muamvatin showed a small M+H ion at *m/z* 395. Fragment ions at *m/z* 377 and *m/z* 359 represented loss of two water molecules. Based on mass spectral data, the molecular formula $C_{23}H_{38}O_5$ was deduced. A strong absorption at 236 nm in UV spectrum suggested the presence of a 1,3-diene. The polypropionate nature of muamvatin was clearly indicated in its ^{1}H NMR spectrum showing six methyl groups, two ethyl groups, two exchangeable hydroxyl protons, and the two spin systems **45** and **46** illustrated in **Figure 1.7**. The ^{1}H-^{1}H spin decoupling and COSY experiments, defined two ethyl groups, one at each terminus, with one connected to a vinylic carbon and the other one attached to a carbon bonded to oxygen (C1-C2 and C17-C18). Correlations between the protons at C5 to those at C4 and C6 were clear in the COSY spectrum. A ^{1}H-^{13}C NMR correlation experiment allowed assignment of all protonated carbons. The five remaining quaternary carbons were assigned to two fully substituted sp^2 carbons and three ketal carbons. The above data supported the partial structure **47** because of no clear differentiation among ketal carbons (**Figure 1.7**). A NMR ^{1}H-^{13}C polarization transfer experiment completed the structure assignment by correlating the proton at C5 to both the C7 and C3 ketal carbons.

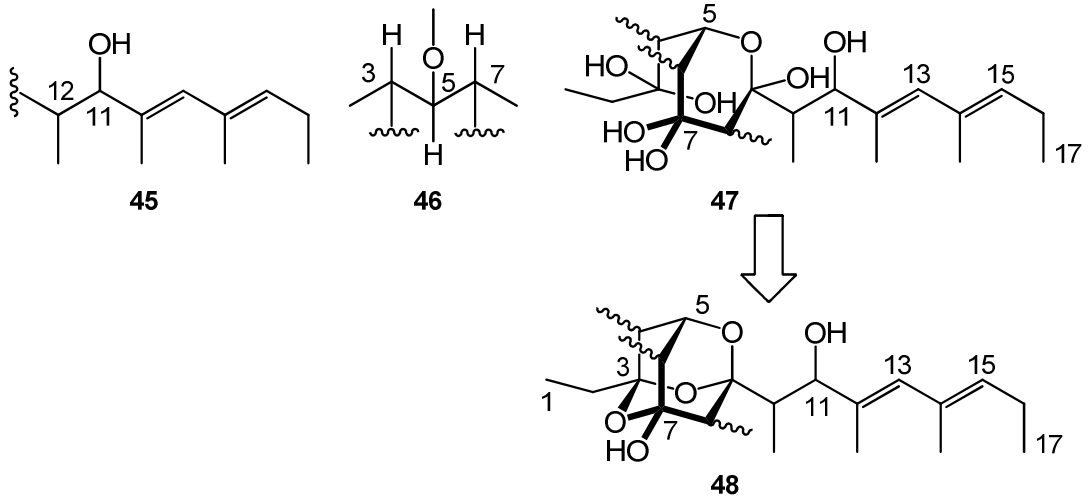
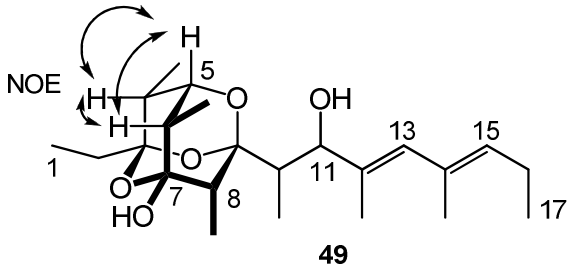


Figure 1.7 Proposed fragments of muamvatin defined by NMR experiments

The relative configuration of the substituents on the trioxaadamantane ring system was defined based on proton-proton coupling constants and two dimensional NOE experiments. The small $^{3}J_{HH}$ couplings between H-C5 and H-C4, and H-C5 and H-C6 are due to axial-equatorial-axial orientation made clear from COSY and NOE between H-C4 and H-C6. Comparative NMR studies as well as the rigidity of the trioxaadamantane ring system forced the ethyl group at C3, hydroxyl group at C7, and the diene side chain to have equatorial orientation. Clear NOE correlation between H-C8 and the C6 methyl group indicated that the C8 methyl group was axial. The *E* geometry of the two trisubstituted olefinic carbons was assigned based on the ^{13}C NMR shifts of the vinylic methyls at δ 12.3 and 16.7 ppm but the relative configuration at C10 and C11 remained undefined (**Figure 1.8**). The PCC oxidation of **49** produced aldehyde **50**.[30] High resolution FABMS of **50** secured the molecular formula as $C_{15}H_{24}O_5$ which was in agreement with the ^{1}H and ^{13}C NMR and confirmed the structure of **50** with the exception of C10 relative configuration (**Scheme 1.4**).

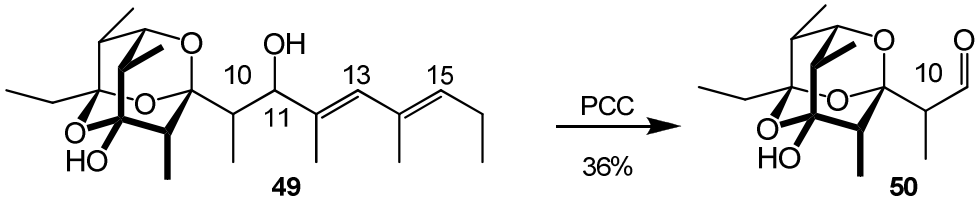


49

Figure 1.8 NMR based correlation of substituents on muamvatin backbone structure

The above NMR studies defined clearly the three-dimensional structure of muamvatin (except for the relative configuration of the two stereogenic centers at C10 and C11); however, the absolute configuration of the natural product remained unknown. In contrast with its unique structural features, muamvatin did not show any antibiotic activity against any common test organisms.

Scheme 1.4 Oxidative degradation of muamvatin (**49**)



49 **50**

1.4 Synthetic studies on muamvatin

From a synthetic point of view, the key structural features of muamvatin (**30**) include the densely oxygenated octapropionate backbone that contains several contiguous stereogenic centers as well as the unprecedented trioxaadamantane ring system. This ring system has subsequently been found in only one other naturally occurring polypropionate, caloudrin B (**29**).[24]

To date, there has been a single total synthesis of muamvatin which confirmed the relative configuration of the trioxaadamantane and established its absolute

configuration.[31] On the other hand, the formation of the unique trioxaadamantane ring system has also been studied.[29,32,33] The details of each will be discussed in following sections.

1.4.1 Hoffmann's studies on muamvatin

Hoffmann's approach to muamvatin started with extensive studies on the trioxaadamantane portion of muamvatin and its formation under different conditions. Their first approach was to make hydroxytrione **52** from triol ketone **53**. Because compound **53** predominantly existed as the hemiacetal **54**, the free hydroxyl group at C5 and ketone at C9 were internally protected. Thus, **54** selectively exposed the hydroxyl groups at C3 and C7 for further oxidation (**Figure 1.9**).

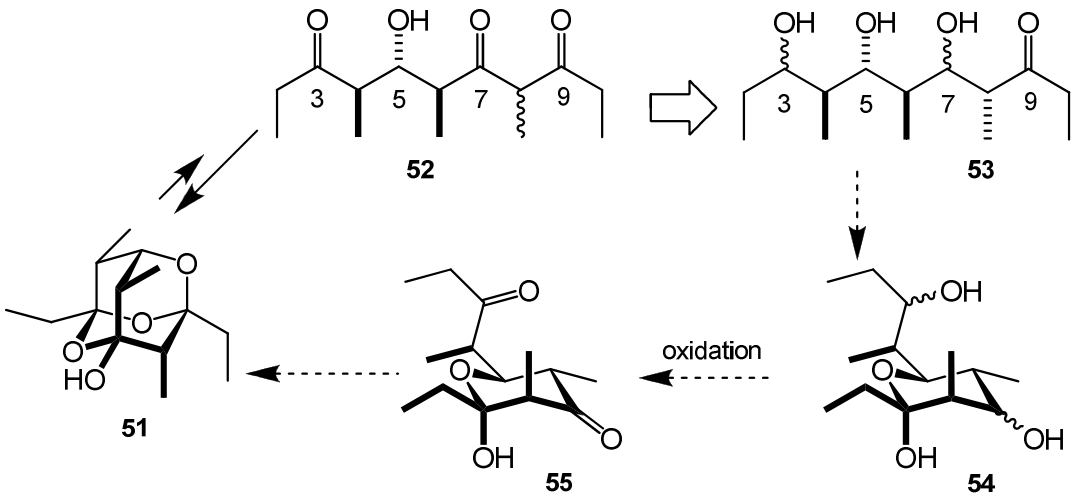
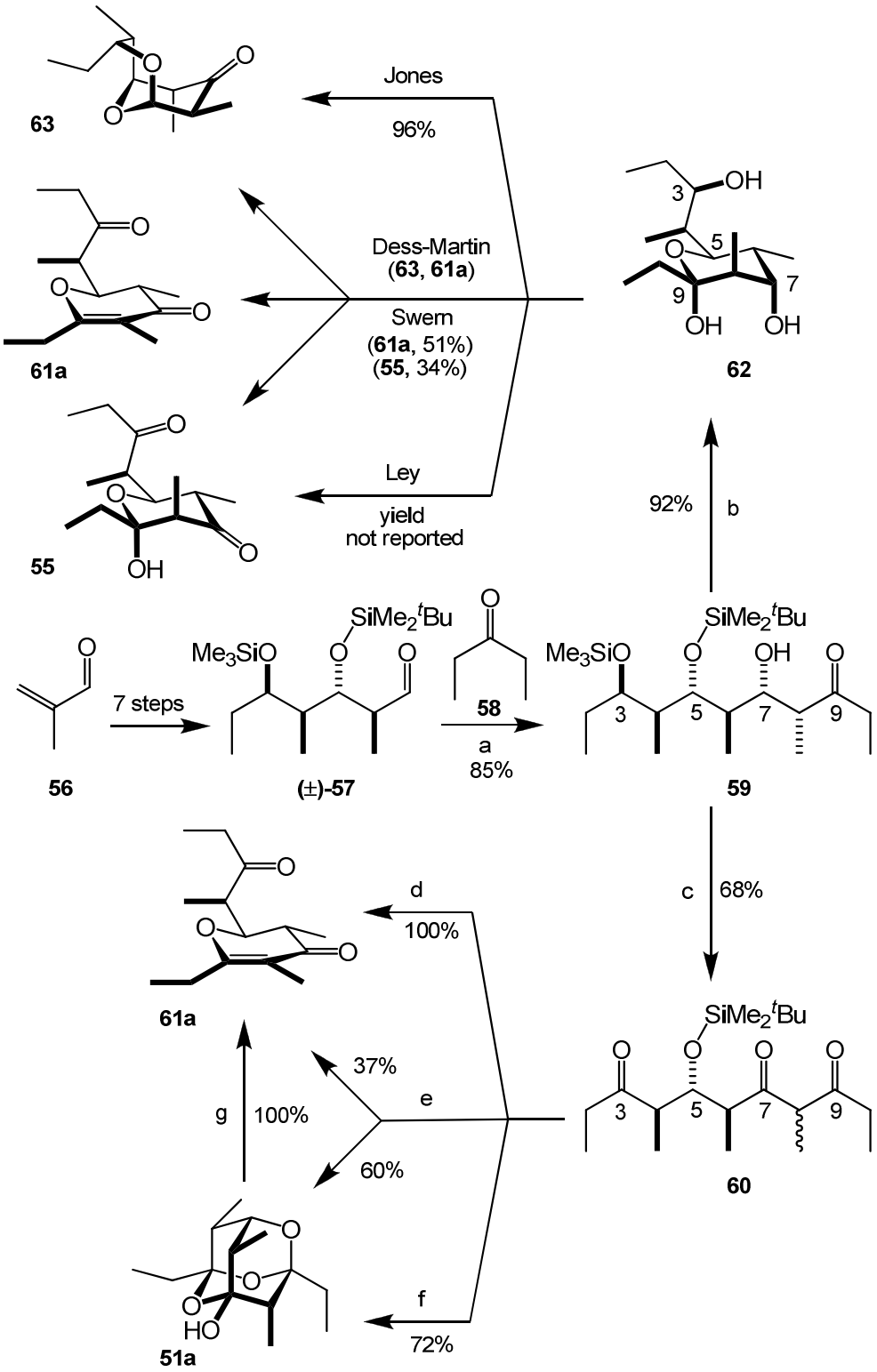


Figure 1.9 Synthetic strategy for making compound **27**

The aldehyde (±)-**57** was obtained in 7 steps from methacrolein **56** in a racemic form.[34] Boron mediated aldol reaction of (±)-**57** with 3-pentanone (**58**) formed **59** as a single compound in 85% yield establishing all stereogenic centers required on the carbon skeleton. Liberating the hydroxy groups at C3 and C5 produced the hemiacetal **62** in 92%

yield. Because several attempted methods to convert **62** to **55** were not effective, a new approach to the same target was devised. Direct Swern oxidation of **59** gave trione **60** in 68% yield as a mixture of epimers at C8 (**Scheme 1.5**). Hydrolysis of the C5 silyl ether in **60** under acidic conditions quantitatively formed dihydropyrone **61**. Using less acidic HF·pyridine to remove the silyl ether formed 60% of the desired trioxaadamantane **51** and 37% of **61**. Optimized reaction conditions gave the trioxaadamantane ring **51** in 72% yield with no elimination product. Exposing **51** to acidic conditions also gave dihydropyrone **61**. This approach showed that both epimers of **60** can form the desired trioxaadamantane **27**.[34] The cyclization conditions found in this study were used in a separate investigation to establish the absolute configuration of muamvatin.

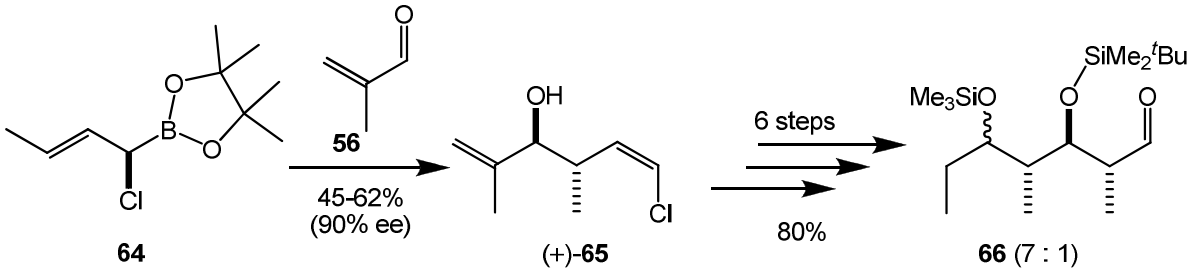
Scheme 1.5 Hoffmann's approach to the trioxaadamantane ring system **51**



a) 9-BBNOTf, $^{i}Pr_2EtN$; b) $Bu_4N^+F^-$; C) $(COCl)_2$, DMSO, Et_3N; d) HF, CH_3CN; e) HF·Py, 65 ºC; f) HF·Py, THF, H_2O, 20 ºC; g) 1N aq. HCl, CH_3CN.

Hoffmann et al. successfully synthesized both C10 epimers of aldehyde **50**, the degradation product from PCC oxidation of **49**.[35] Coupling of (*R*)-α-chlorocrotylboronate **64** with methacrolein (**56**) formed alcohol (+)-**65** that after stereoselective chain elongation and oxidation state adjustments, provided aldehyde **66** in 6 steps and 80% overall yield (**Scheme 1.6**).[34]

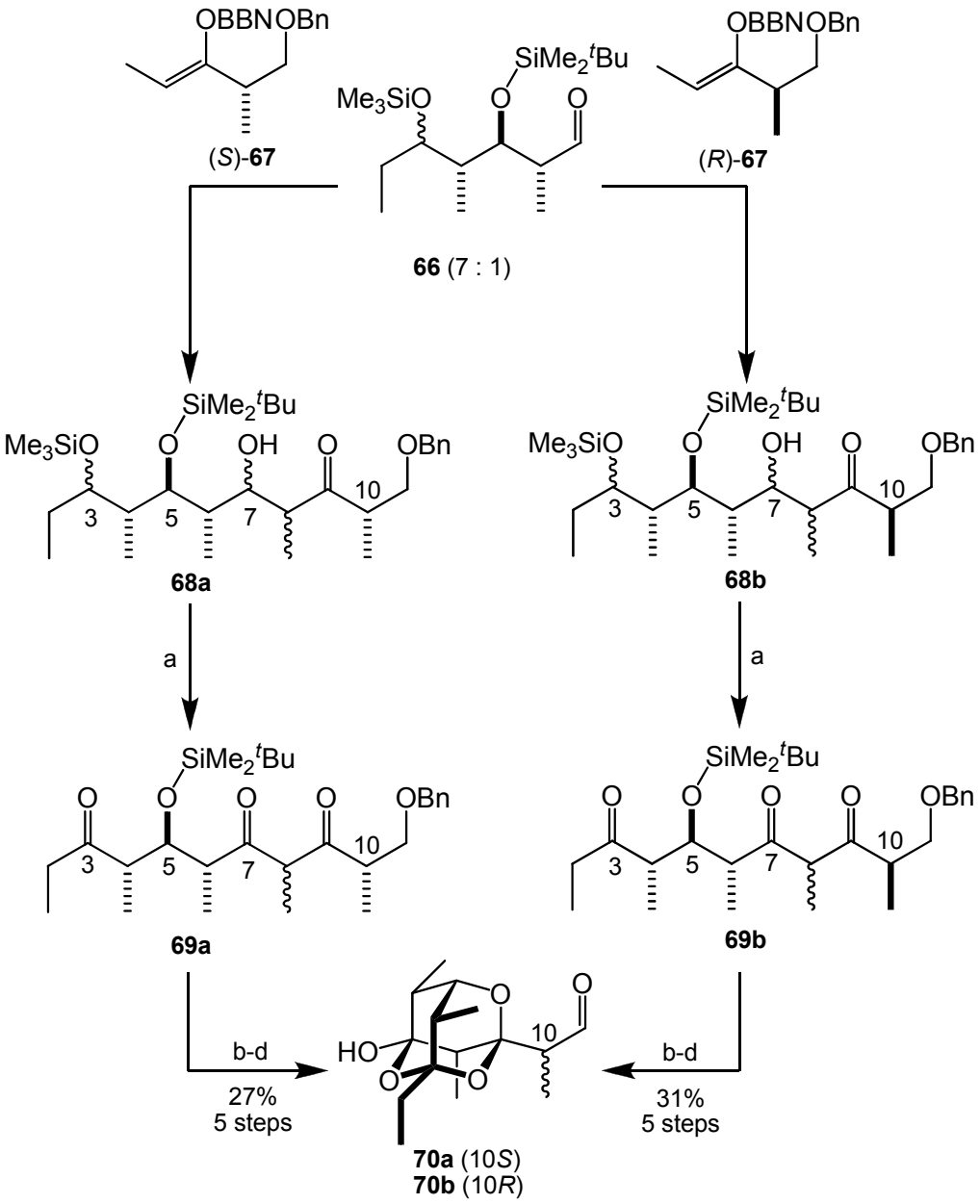
Scheme 1.6 Enantioselective synthesis of aldehyde **66**



Boron mediated aldol couplings of aldehyde **66** with each enantiomer of **67** formed aldol adducts **68a** and **68b** (**Scheme 1.7**). Swern oxidation of the aldol adducts according to the previously developed method (**Scheme 1.5**), gave triones **69a** and **69b**, respectively. Subjecting the triones to HF·pyridine followed by hydrogenolysis of the benzyl protecting group and oxidation of the liberated alcohol groups gave aldehydes **70a** and **70b**.

The spectroscopic data for **70a** perfectly matched those for aldehyde **50**, the degradation product from muamvatin. In addition, the single crystal X-ray structure for **70a** established the relative configuration for all stereogenic centers. Finally, the optical rotations for aldehydes **70a** and **50** had opposite signs establishing the absolute configuration of **50** as *ent*-**70a**.

Scheme 1.7 Preparation of both C10 epimers of aldehyde **70**



a) $(COCl)_2$, DMSO, Et_3N; b) HF·Py, THF, H_2O, 20 ºC; c) H_2, $Pd(OH)_2$; d) PCC/aluminum oxide.

Hoffmann proposed the relative configuration of the hydroxy group at C11 of muamvatin based on the available NMR data of the natural product and knowing the relative configuration at C10. The torsion angle around the C9-C10 bond is dictated by

minimizing the g^+g^- interactions between the methyl groups at C10 and C8. On the other hand the C10-C11 torsion angel in muamvatin should have a conformation that minimizes g^+g^- interactions as well as allows hydrogen bonding between the hydroxyl group at C11 and one of the oxygens at C9 ketal moiety. Therefore, among the possible C10-C11 *syn* and *anti* diastereomers of muamvatin only one can explain the large $^3J_{\text{H- C10/ H-C11}}$ coupling constant (J = 9 Hz). Thus, Hoffmann et al. proposed **30** as the structure for muamvatin (**Figure 1.10**).[35]

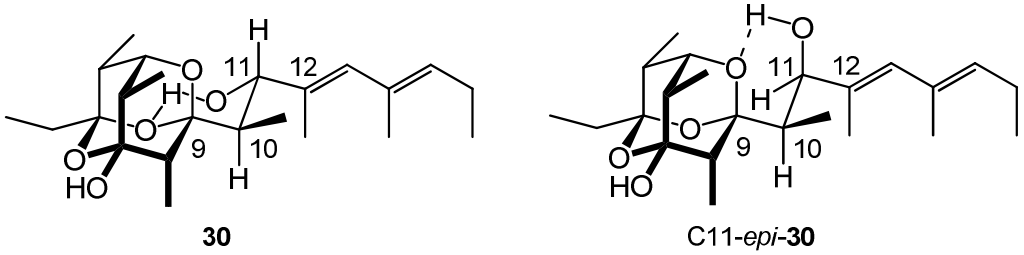


Figure 1.10 Absolute configuration of muamvatin

Extending the above study, Hoffmann et al. attempted the total synthesis of *ent*-muamvatin.[32] The approach was based on the previous studies focused on preparation of the trioxaadamantane ring system of *ent*-muamvatin. Unraveling the full carbon skeleton of *ent*-muamvatin revealed the linear octapropionate chain **71** that was envisioned to arise from ketone **72** and known[34] aldehyde **66**. Ketone **72** was planned to be obtained from aldehyde **73** (**Figure 1.11**).

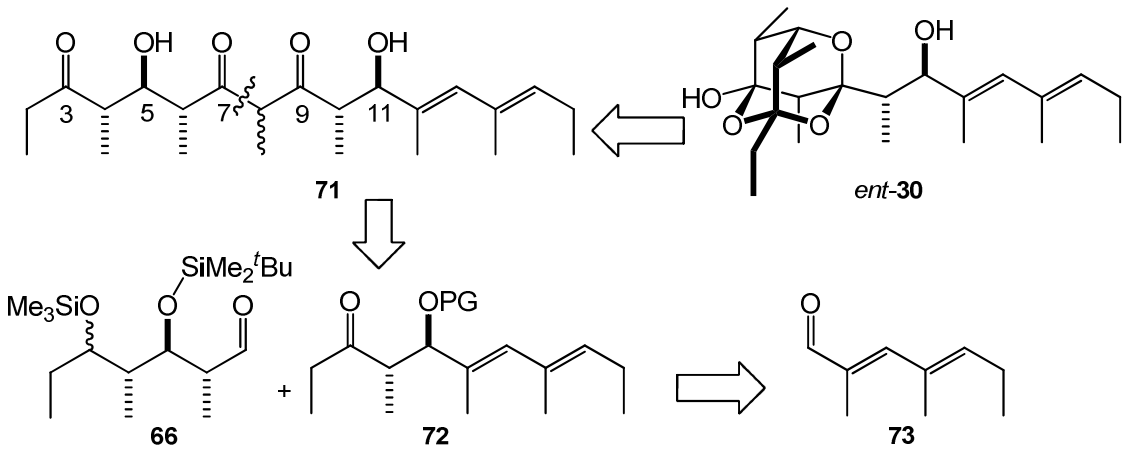
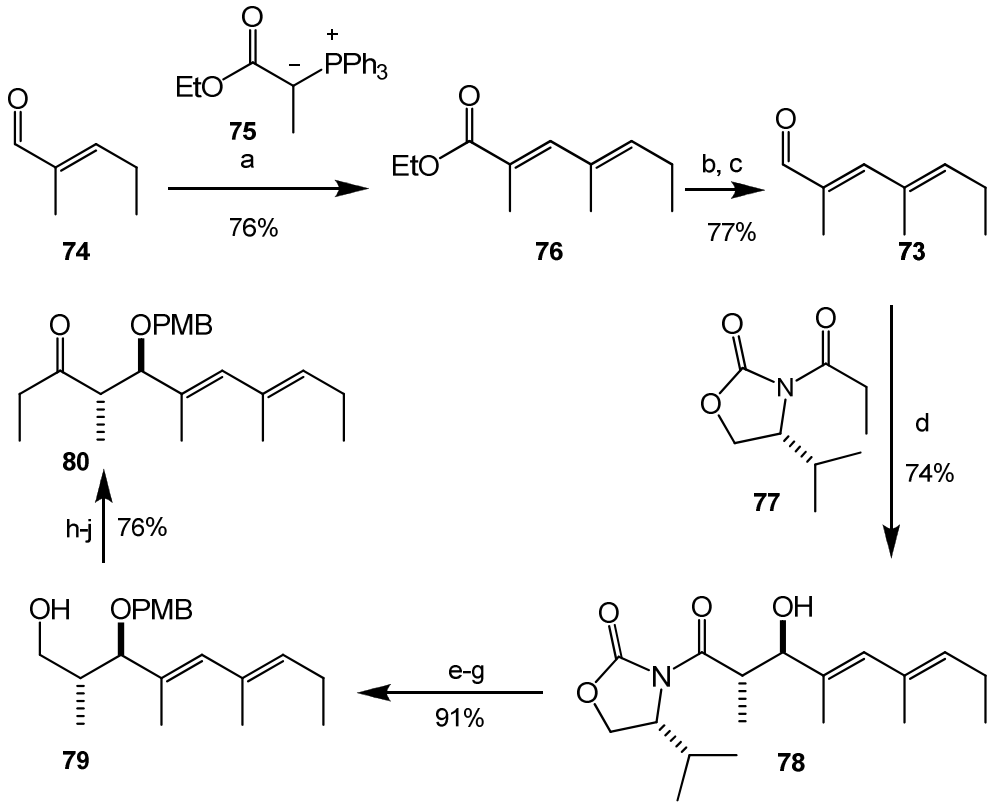


Figure 1.11 Hoffmann's retrosynthetic analysis of *ent*-muamvatin

Aldehyde **73** was prepared in three steps from **74** via Wittig reaction with **75** followed by a sequential redox process. Ketone **80** was obtained from **73** via Evans aldol reaction that set the two required stereogenic centers to give **78** which then was followed by insertion of an ethyl group (**Scheme 1.8**).

Scheme 1.8 Preparation of ketone **80**

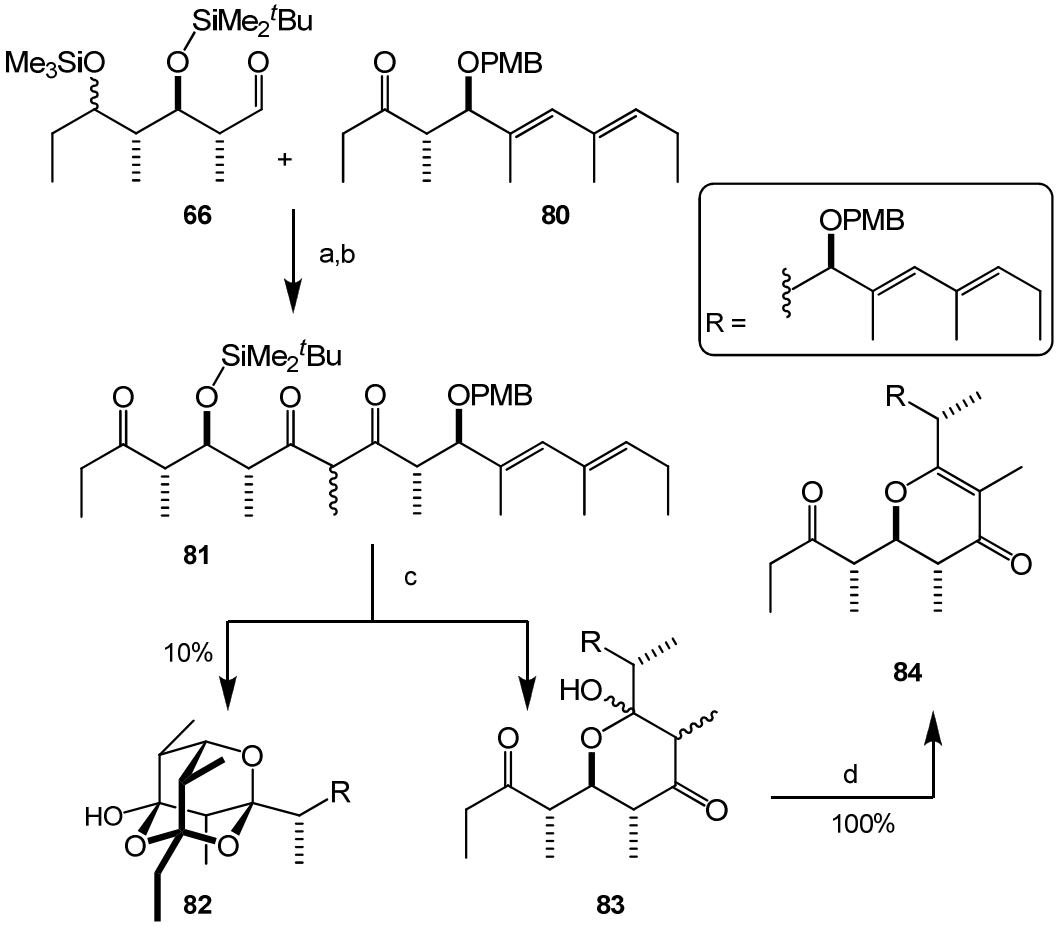


a) THF, reflux; b) $LiAlH_4$; C) $^{n}Pr_4NRuO_4$, NMO; d) Bu_2BOTf, $^{i}Pr_2EtN$; e) $LiBH_4$, MeOH; f) α,α,4-trimethoxytoluene, PPTS; g) DIBAL-H; h) $(COCl)_2$, DMSO, Et_3N; i) EtMgBr; j) $(COCl)_2$, DMSO, Et_3N.

Boron mediated aldol reaction of ketone **80** with aldehyde **66** followed by oxidation of the newly formed hydroxy group gave **81**, as a protected derivative of the acyclic tautomer of *ent*-muamvatin. Treatment of **81** with HF·pyridine affected removal of the silyl protecting group of the C5 hydroxy group and catalyzed formation of the trioxaadamantane ring generating **82** in 10% yield along with hemiacetal **83**. Further efforts to form **82** from **83** were unsuccessful and at best resulted in dehydration to dihydropyrone **84** (**Scheme 1.9**). On the other hand, attempts at oxidative removal of the PMB group in **82** failed to produce the desired *ent*-**30**. Because the goal of this work was

to establish the structure of muamvatin, additional research to solve the above problem was not pursued after Paterson's report of the total synthesis of muamvatin **30**.[31]

Scheme 1.9 Assembly of the full carbon skeleton



a) 9-BBNOTf, $^{i}Pr_2EtN$; b) $(COCl)_2$, DMSO, Et_3N; c) HF·Py, THF, H_2O, 20 ºC, 8 days; d) PTSA.

Although Hoffmann's approach to muamvatin was not successful, his approach successfully established the absolute and relative configuration of all stereogenic centers on the carbon backbone of muamvatin.

1.4.2 Paterson's total synthesis of muamvatin

Paterson et al. reported the only total synthesis of muamvatin.[31] Because the absolute and relative configuration of muamvatin was not known at the time, the initial goal was to prepare aldehyde **50**[30] (*ent*-**70a**), obtained by Ireland et al. as a degradation product from muamvatin. According to their retrosynthetic analysis (**Figure 1.12**), aldehyde *ent*-**70a** would be obtained by sequential aldol coupling of propanal (**87**) with the dipropionate reagent (*R*)-**86**. Oxidation state manipulation of the resulting pentapropionate **85** would set the stage for cyclization of the trioxaadamantane ring system.

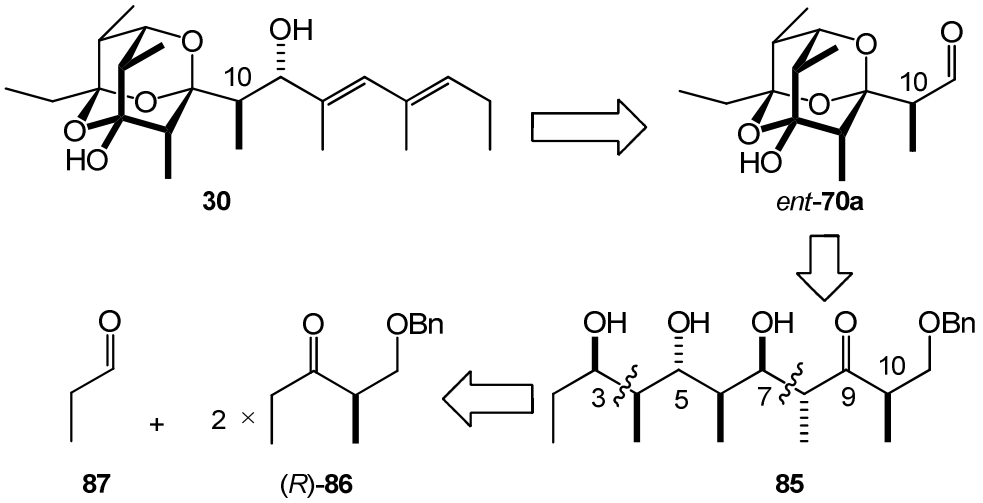
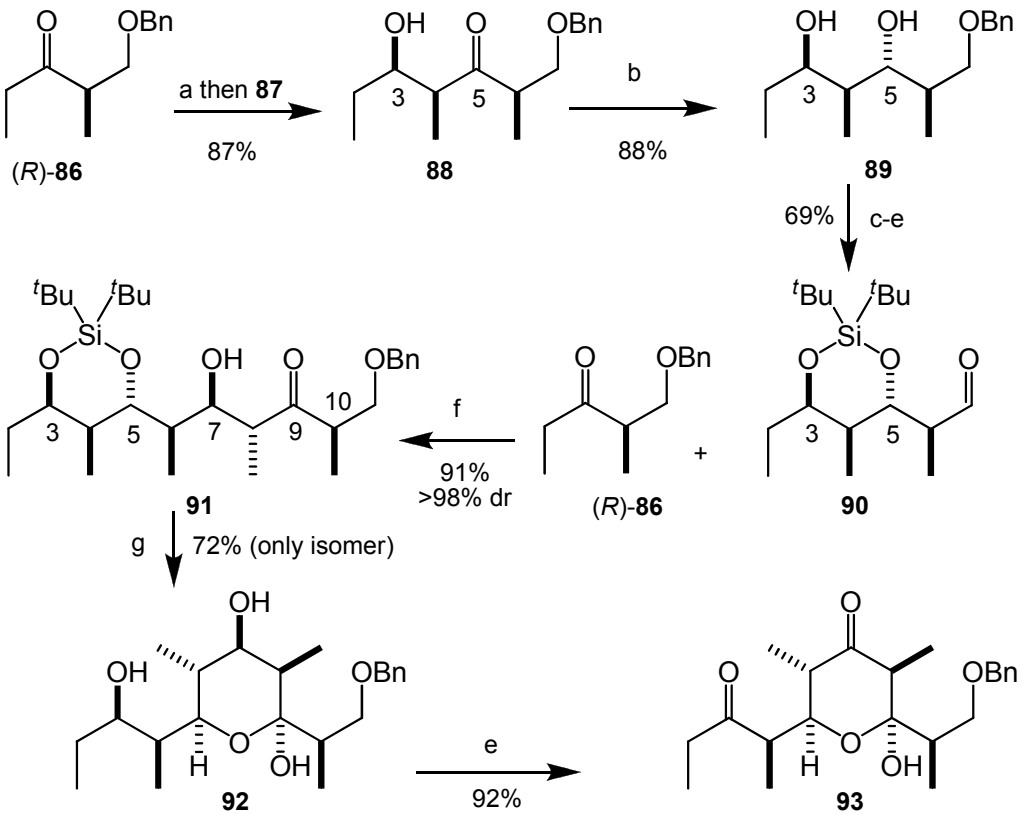


Figure 1.12 Paterson's retrosynthesis of muamvatin **30**

Diastereoselective aldol reaction of the Sn(II) enolate of (*R*)-**86** with propanal formed **88** (**Scheme 1.10**). Stereoselective reduction of ketone **88** followed by protection of the diol, debenzylation, and oxidation of the resulting primary alcohol produced aldehyde **90**. Diastereoselective boron mediated aldol reaction of ketone (*R*)-**86** with aldehyde **90** formed the desired pentapropionate **91**. Deprotection of the silyl group formed hemiacetal **92** as the only product. Due to internal protection of the hydroxyl

group at C5 in the hemiacetal **92**, selective oxidation of hydroxyl groups at C3 and C7 was successfully achieved by Swern oxidation. Diketone **93** was sensitive to acidic and basic conditions but eventually was successfully cyclized to the trioxaadamantane **98** by overnight exposure to silica gel (**Scheme 1.11**).

Scheme 1.10 Synthesis of diketone **93**

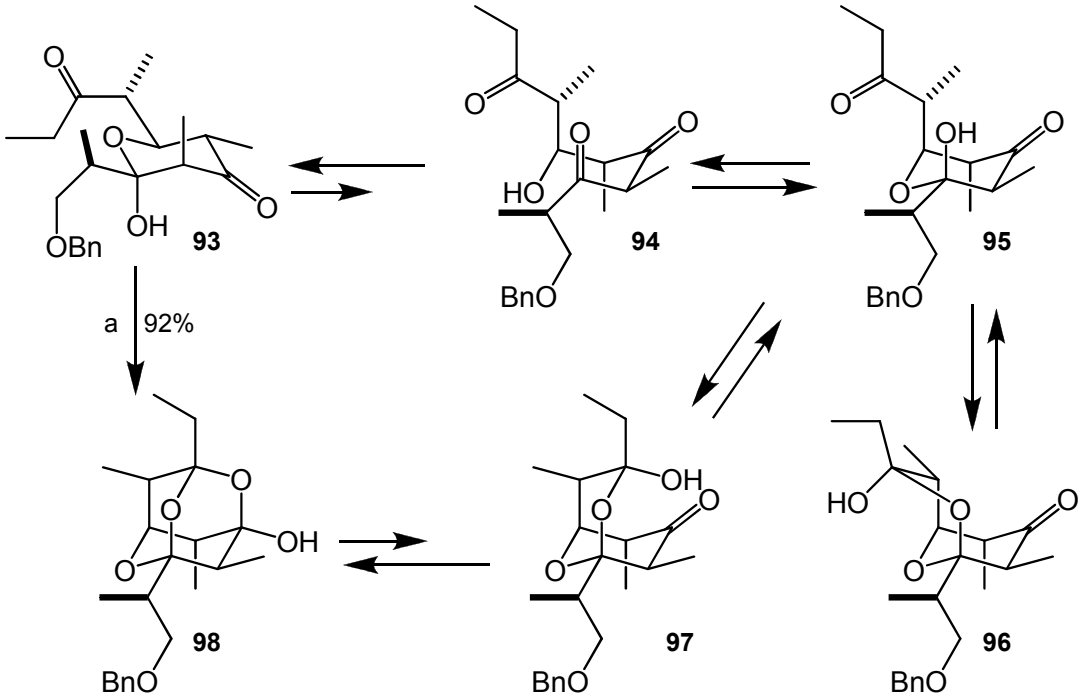


a) $Sn(OTf)_2$, Et_3N; b) $Me_4NBH(OAc)_3$; c)$tBu_2Si(OTf)_2$, 2,6-Lutidine; d)H_2, 10% Pd/C; e) $(COCl)_2$, DMSO, Et_3N; f) $(Chx)_2BCl$, Et_3N; g) HF·Py, THF.

Rearrangement of hemiacetal **93** to the desired ring system **98** required ring opening of the hemiacetal ring system to the hydroxyl triketone **94** followed by a series of acetal ring forming steps (**Scheme 1.11**). Because this rearrangement was successfully

catalyzed by silica gel, the possibility that muamvatin was an artifact of isolation was suggested.

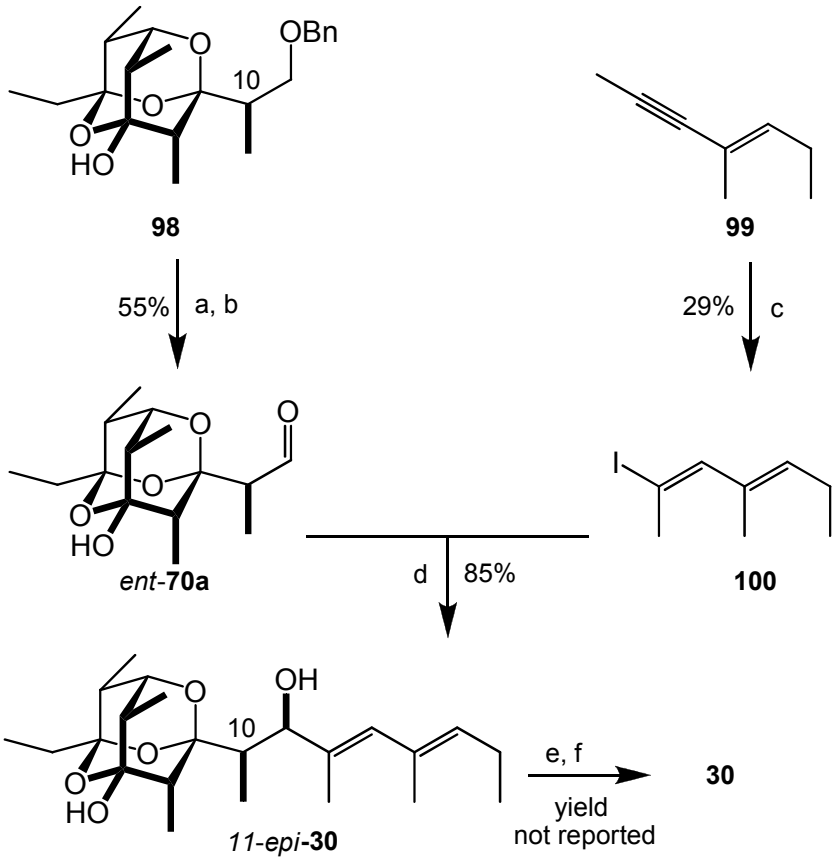
Scheme 1.11 Formation of the trioxaadamantane **98**



a) SiO_2

Trioxaadamantane **98** was readily converted to aldehyde *ent*-**70a** by hydrogenalysis of the benzyl ether followed by PDC oxidation of the resulting alcohol (**Scheme 1.12**). Coupling aldehyde *ent*-**70a** with the vinyl lithium reagent formed by treatment of **99** with ^{t}BuLi gave 11-*epi*-muamvatin in 85% yield. The C11 configuration was inverted via an oxidation, stereoselective reduction sequence to give muamvatin (**30**) (**Scheme 1.12**). This synthesis successfully established the absolute and relative configuration of muamvatin however the overall yield was not reported.

Scheme 1.12 Completion of the total synthesis of muamvatin (**30**)



a) H_2, 10% Pd/C; b) Pd/C, 4-Å molecular sieve; c) catecholborane, chloroamine-T, NaI; d) ^{n}BuLi; e) $^{n}Pr_4NRuO_4$, NMO; f) DIBAL-H.

1.4.3 Studies on formation of the trioxaadamantane ring system under thermodynamic control

The unusual trioxaadamantane ring has been observed in only two natural products: muamvatin (**30**) and caloundrin B (**29**). The difference between these trioxaadamantane ring systems is the relative configuration at C4 (i.e., (4*R*) in muamvatin (**30**) and (4*S*) in caloundrin B (**29**)). Formation of each ring system requires a specific cyclization mode of its linear putative precursor among all other possible modes of cyclization (see **Figure 1.13** and **Figure 1.14**). In this regard, theoretical ground state energies of the possible hemiacetal, spiroacetal, and trioxaadamantane ring systems that

might be formed from the putative acyclic precursor of siphonarine B (**28**), muamvatin (**30**), and caloundrin B (**29**) were calculated by Garson et al.[29] They proposed that thermodynamic factors control the formation of muamvatin and the siphonarins, where the preferred acetal ring systems are correlated to the configuration of the hydroxyl and methyl groups and the oxidation state of the carbons in the acyclic precursor.

The acyclic tautomer of muamvatin is shown in two C8-epimeric forms in **Figure 1.13**. Two different cyclization modes result in trioxaadamantanes (**30** and 8-*epi*-**30**) or spiroketals (**101a** and **101b**). Molecular mechanics calculations indicated the trioxaadamantane ring system **30** is significantly more stable than the other possible structural isomers (i.e., 8-*epi*-30, hemiacetal **102**, **101a**, and **101b**). These results supported the idea that muamvatin could be formed in a thermodynamically controlled non-enzymatic process and was a possible artifact of isolation. In other words, the actual biosynthetic product might be the less stable hemiacetals **101a**, **101b**, or **102** or one of the acyclic epimers *ent*-**71** which then formed the trioxaadamantane **30** via exposure to silica gel chromatography during isolation.

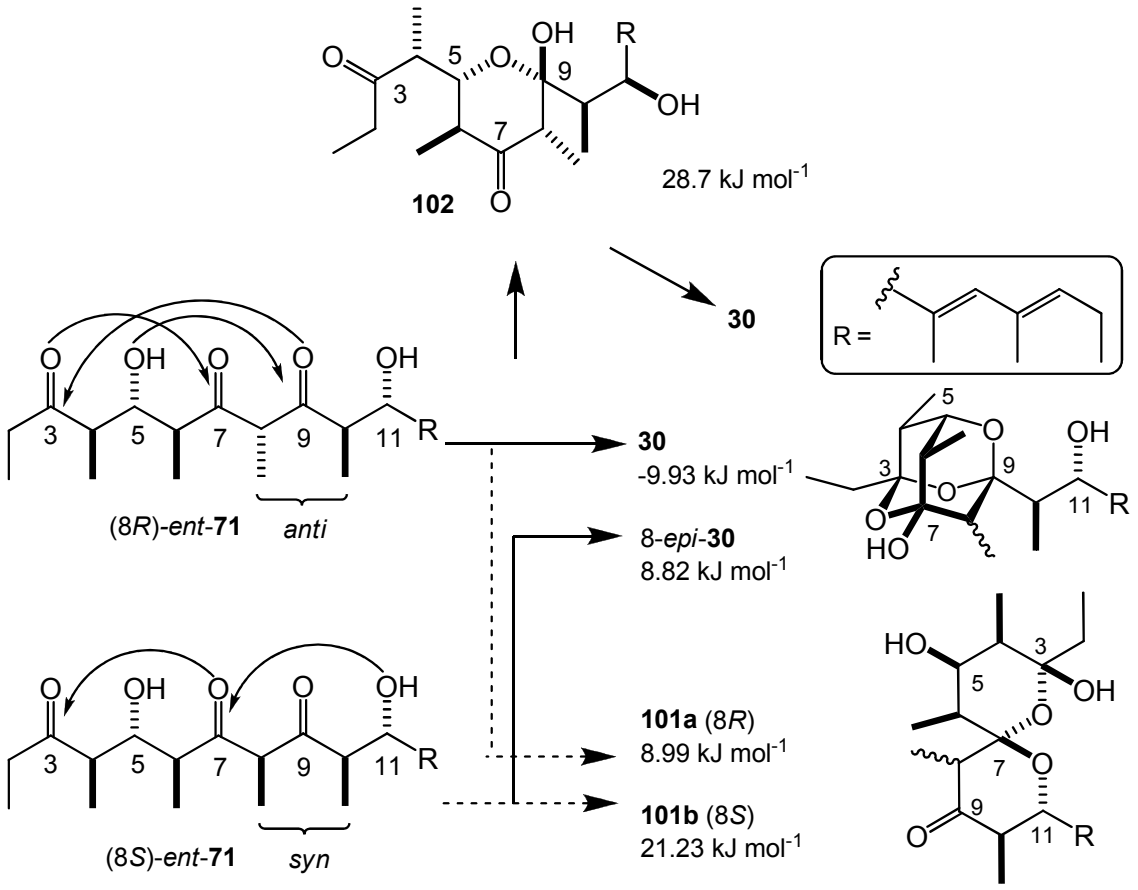


Figure 1.13 Various cyclization modes of the acyclic tautomer of muamvatin

Similar calculations were performed to compare the relative energies of the possible spiroacetal and trioxaadamantane resulting from cyclization of the common ring-chain tautomer of caloundrin B (**29**) and siphonarin B (**28**) (**Figure 1.14**). These results suggested a much higher relative stability of the spiroacetal structures (**28** and (8*S*)-**28**) over the trioxaadamantane ring systems (**29** and (8*R*)-**29**) the same as what was shown by Ward et al.[10,11] experimentally. Spiroacetal **28** (siphonarin B) was calculated to be slightly more stable than its epimer (8*S*)-**28** (destabilized by a g^+g^- interactions between the methyl group at C6 and C8). Similarly, comparing the relative stability of **29** and 8-*epi*-**29** showed that **29** is 5.33 kJ mol^{-1} more stable than 8-*epi*-**29** due to the 1,3-diaxial interaction between methyl groups at C6 and C8 in 8-*epi*-**29**.

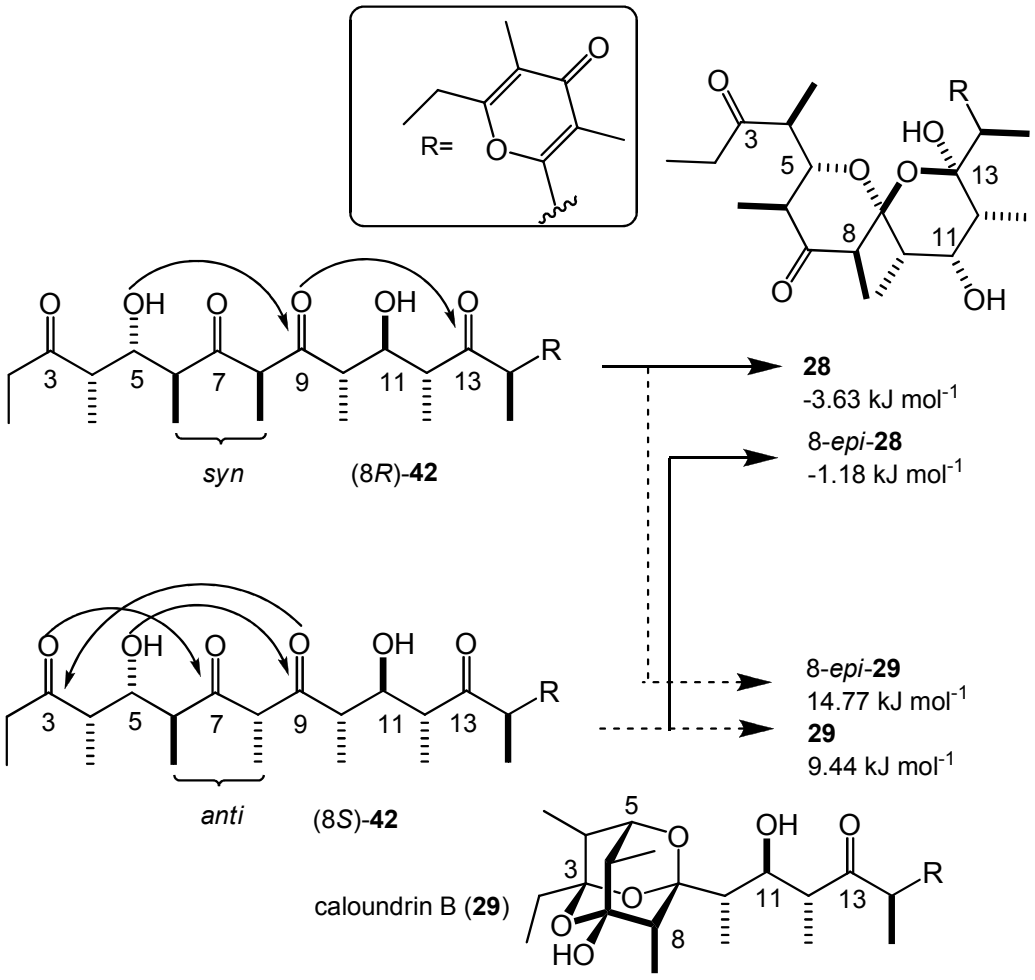


Figure 1.14 Siphonarin B (**28**) *vs.* caloundrin B (**29**) cyclization

Recently, Beye and Ward were able to synthesize a mixture of the putative precursors (8*R*)-**42** and (8*S*)-**42** (**Figure 1.6**).[10] Interestingly, they successfully isomerized this epimeric mixture into siphonarin B (**28**), baconipyrone A (**43**), and baconipyrone C (**44**); however, no sign of caloundrin B (**29**) was observed in these experiments. In a separate study, Becerril-Jimènez and Ward prepared *ent*-caloundrin B by total synthesis.[11] They showed that *ent*-caloundrin B was thermodynamically unstable relative to *ent*-siphonarin B (**28**).[11] It was proposed that the actual biosynthetic product might be caloundrin B (**29**) and that the other isomeric products (**28**, **43**, and **44**) are possible artifacts formed in the isolation process.

Beye and Ward also successfully synthesized truncated models of the trioxaadamantane ring systems of muamvatin (**30**) and caloundrin B (**29**) and studied their thermodynamic behaviors (**Scheme 3.11**).[73] The model trioxaadamantane ring systems of muamvatin (**30**) and caloundrin B (**29**), **51a** and **51b**, respectively, are ring-chain tautomers of the hydroxytriones **103a** and **103b** (**Figure 1.15**). Although the trioxaadamantane ring systems are the thermodynamically most stable tautomers, their formation proceeds through the less stable hemiacetal intermediates **105a** and **105b**. Any harsh acidic or basic conditions can turn these hemiacetals to dihydropyrones (**61a** and **61b**) by dehydration or induce retro-Claisen fragmentation to give esters (**106a** and **106b**).

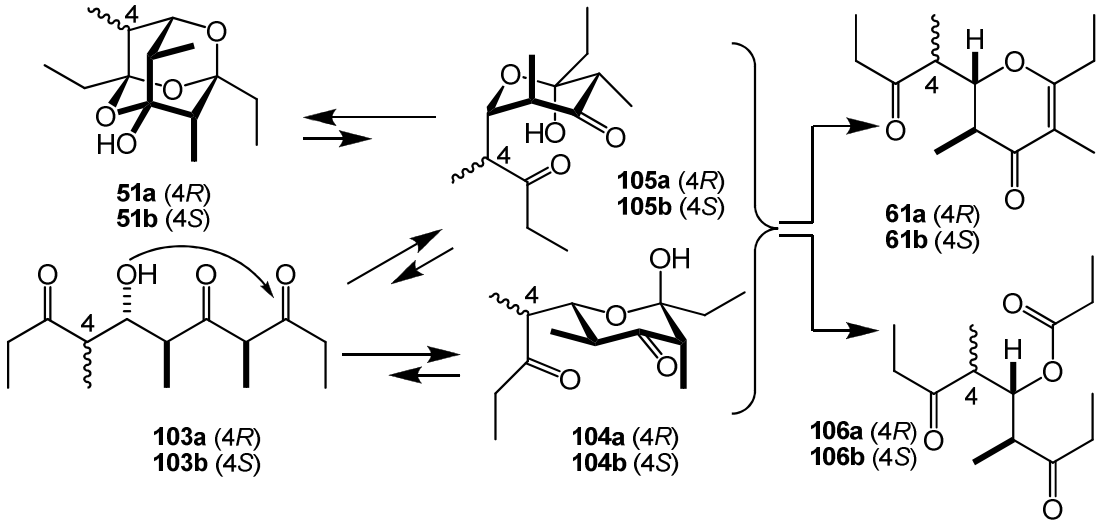
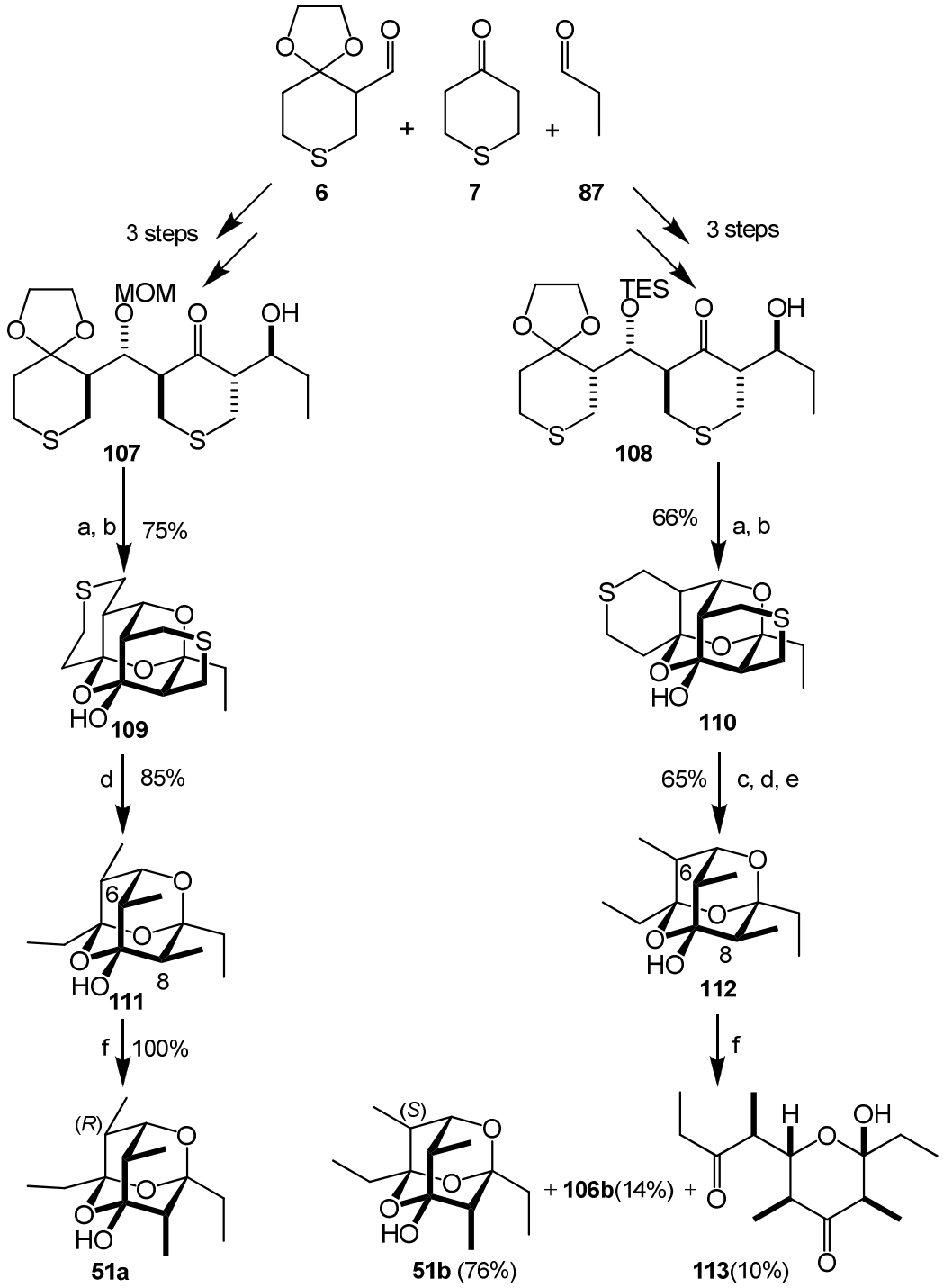


Figure 1.15 Trioxaadamantanes from 3-hydroxy-1,5,7-triones

The dithiatrioxa pentacyclic ring systems **109** and **110** were prepared via the thiopyran route to polypropionates (**Scheme 1.13**). Subsequent desulfurization formed the two trioxaadamantanes **111** and **112** that are destabilized by a *syn* pentane interaction between the methyl groups at C6 and C8. The isomerizations of **111** and **112** to the more

stable epimers **51a** and **51b** respectively were achieved by treatment with imidazole. This isomerization required ring opening, epimerization of C8 methyl group (to form acyclic precursors **103a** and **103b**) and refolding as indicated in **Figure 1.15**. Interestingly, the isomerizations of **111** and **112** showed quite different behaviors. The trioxaadamantane ring system **111** quantitatively formed the thermodynamically more stable trioxaadamantane **51** on exposure to imidazole. Isomerization of **112** under the same condition formed trioxaadamantane **51b** along with the hemiacetal **113** and ester **106b** (the result of retro-Claisen fragmentation of a hemiacetal forms; e.g. **113**) (**Scheme 1.13**).

Scheme 1.13 Synthetic studies on model trioxaadamantanes from muamvatin (**30**) and caloundrin B (**29**)



a) IBX, DMSO b) $FeCl_3 \cdot SiO_2$ c) Me_3SiOTf d) Raney Ni e) HF·Py f) Imidazole, $CDCl_3$, rt

1.5 Conclusions

The unusual trioxaadamantane ring system of muamvatin has been studied in several research groups. Successful synthesis of **50** and **51** established the absolute and relative configuration of the trioxaadamantane ring system of muamvatin (**30**) and provided strategies and conditions to form the unusual trioxaadamantane ring system. The only total synthesis of muamvatin disclosed by Paterson et al. proved the structure. However, because the synthesis proceeded via a pre-formed trioxaadamantane intermediate, there was no opportunity to study the behavior of acyclic tautomer **42** and its cyclization to **30**. The synthesis of **42** and study of its cyclization behavior would help to answer questions regarding the origin of the unusual ring system in muamvatin (**30**) (whether it is formed via an enzymatic process or is an artifact of isolation). In this regard, Ward et al. developed methodologies for fast, easy, and selective preparation of propionate synthons via the thiopyran route to polypropionates and successfully disclosed total synthesis of several polypropionate natural products.[8-11] With these examples in hand, research was directed towards the synthesis of putative linear precursor of muamvatin and studying its cyclization modes.

2. RESULTS AND DISCUSSION

2.1 Research objectives

The objective of this research was focused on the synthesis of the putative acyclic precursor of muamvatin (**30 = 116a**); i.e., **114a** or its 11-*O*-protected analogue **114b** (**Figure 2.1**). With the acyclic precursor in hand, conditions could be investigated to determine possible cyclization pathways (e.g., formation of the retro-Claisen product **118** or dihydropyrone **117**) and/or facilitate the pathway that leads to the trioxaadamantane **116**. Ideally, such studies should shed light on the possible origin of the unique trioxaadamantane ring system; whether it is formed through an enzyme-mediated process or under thermodynamic control as an artifact of isolation. The previous total synthesis of muamvatin by Paterson et al.[31] (**Section 1.4.2**) established its relative and absolute configuration. Their synthetic approach was based on coupling of a preformed trioxaadamantane fragment *ent*-**70a** with the diene component of the molecule. Although they were able to form the truncated trioxaadamantane ring system **98** successfully, it did not address the origin of the unique ring system present in muamvatin.

The secondary research objective was to demonstrate the synthetic potential of the thiopyran route to polypropionates (see **Section 1.1**) for rapid and stereoselective assembly of the polypropionate motifs.

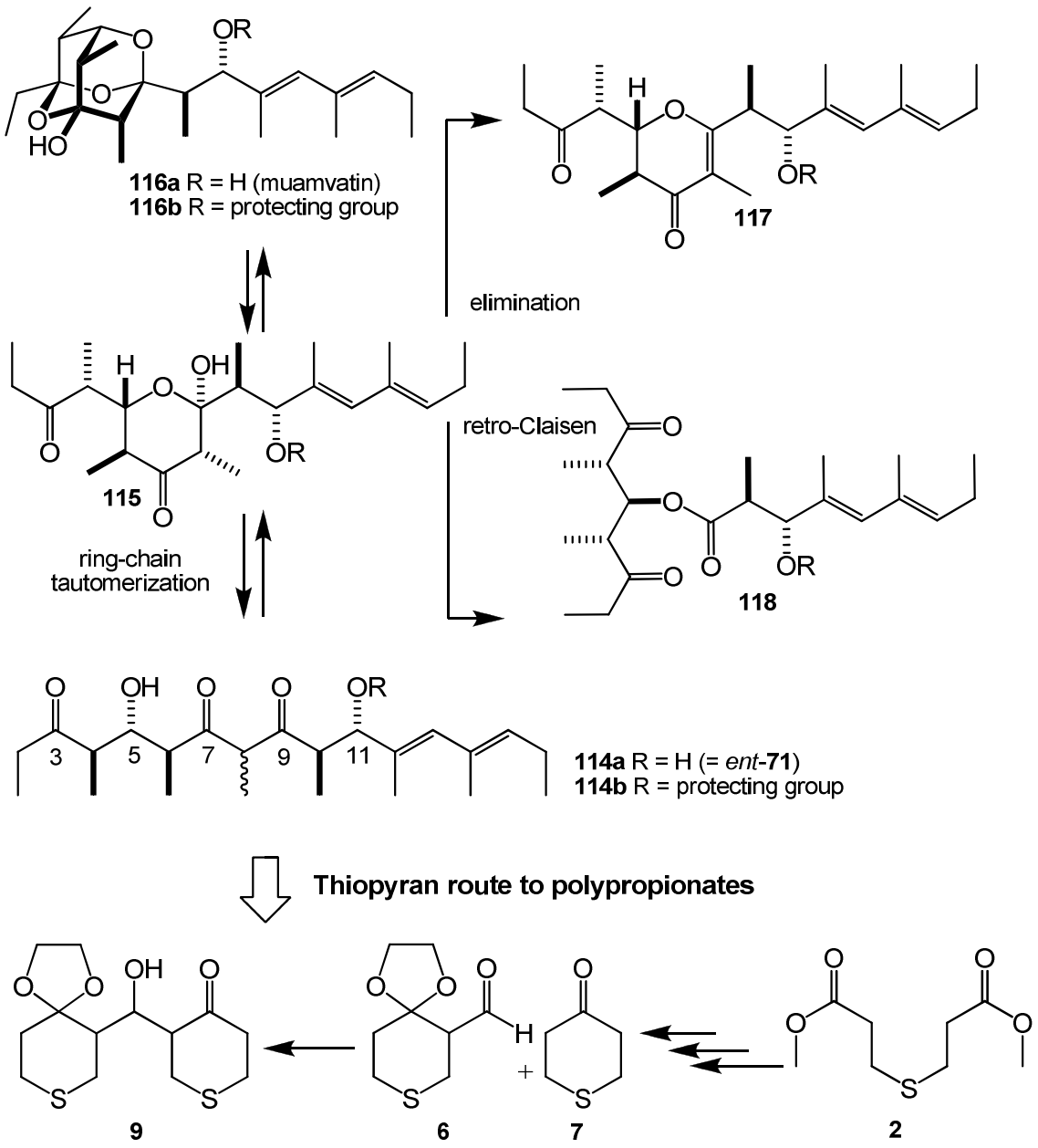


Figure 2.1 Research objectives

2.2 Synthesis of muamvatin, part 1: the thiopyran route

The trioxaadamantane ring system present in muamvatin (**30** = **116a**) is a ring-chain tautomer of the 5,11-dihydroxy-3,7,9-trione (8*R*)-**114a** (**Figure 2.2**). Retrosynthetic disconnections of the C3-C4 and C10-C11 carbon-carbon bonds produce three fragments

that in the synthetic direction were envisioned to be coupled together by substrate-controlled stereoselective aldol couplings. A significant advantage of this synthetic approach is that the aldehyde fragments **87** and **73** are achiral with the triketone **119** as the sole chiral fragment. Thus, either enantiomeric or racemic muamvatin (**116a** = **30**) would be accessible via the same strategy by starting with the appropriate enantiomer or racemic ketone **119**. Of course, trione **119** is expected to be configurationally unstable and a suitable synthetic equivalent would be required. Ketone **9a**, readily available via the thiopyran route to polypropionates, was selected as the reagent to represent **119**. ketones (+)-**9a**, (-)-**9a**, and (±)-**9a** are readily prepared on large scale (40 g) without chromatography via an organocatalytic aldol reaction of ketone **7** with aldehyde (±)-**6**.[3]

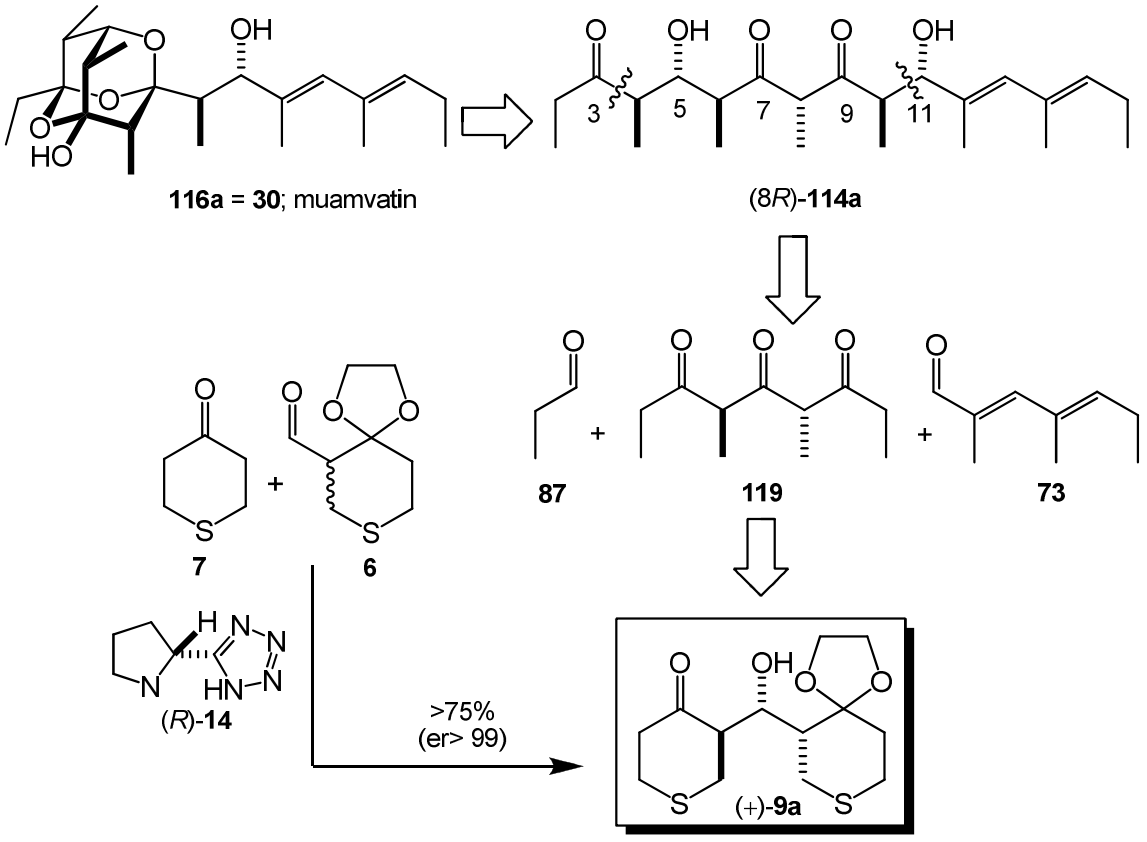


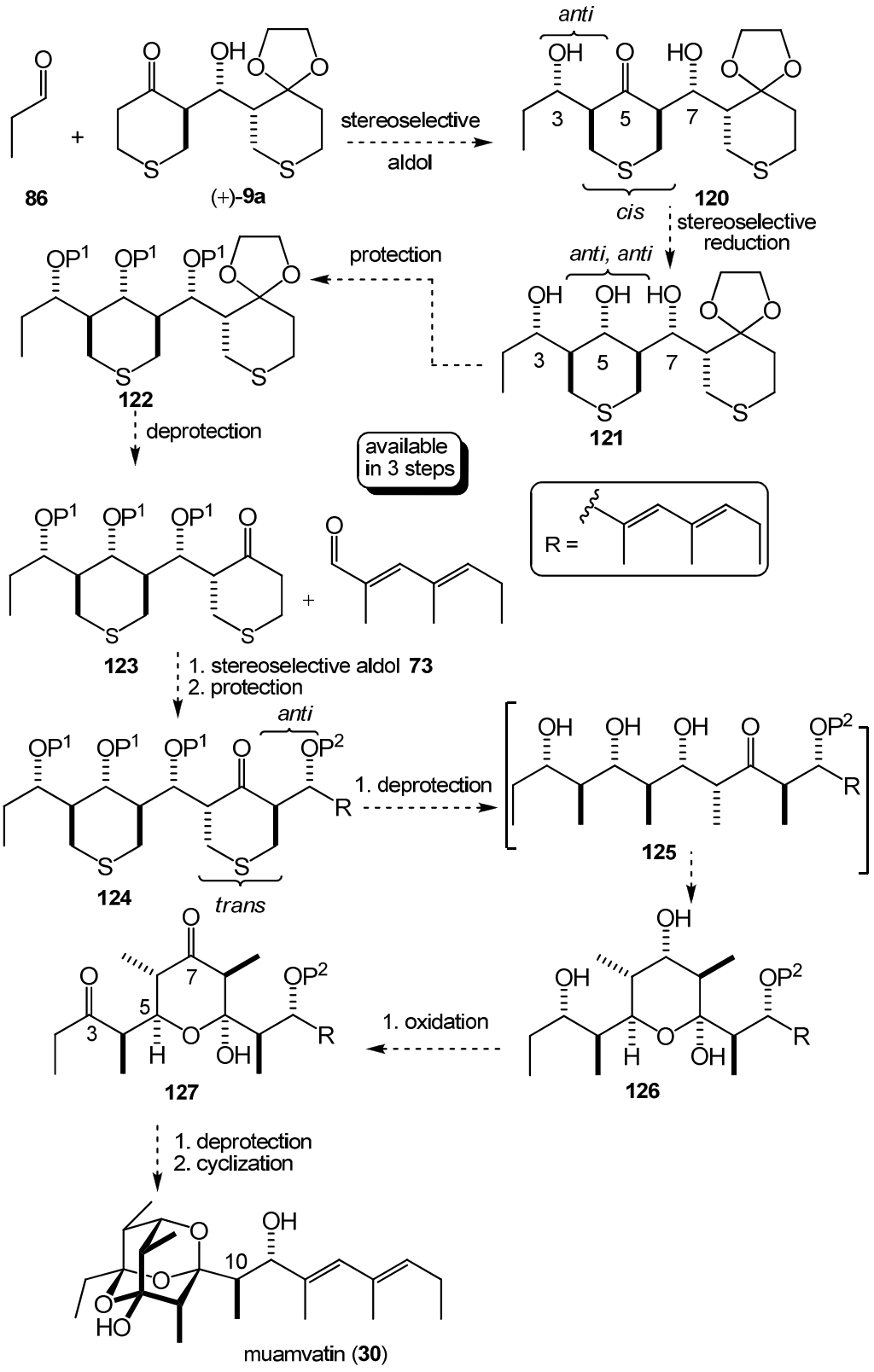
Figure 2.2 Retrosynthetic analysis of muamvatin

Based on the above strategy, a synthetic plan was devised beginning with a stereoselective aldol reaction between propanal (**87**) and ketone (+)-**9a** to set the desired relative configuration at C4 (**Scheme 2.1**). Stereoselective reduction of the C5 ketone moiety of the resulting aldol adduct **120** would result in formation of triol **121**. The second stereoselective aldol reaction of the derived ketone **123** with the known[32] diene aldehyde **73** would form the fully assembled carbon skeleton **124**. Deprotection and desulfurization of **124** would give **125** that was expected to exist in its hemiacetal form **126**. Finally, correction of the oxidation states at C3 and C7 of hemiacetal **126** would furnish the desired target **114** in its hemiacetal form **127**. Successful protecting group manipulation would be critical to the success of this strategy. Not only must protecting group P^1 be orthogonal to protecting group P^2, it must also survive the deprotection of the ketal moiety at C9 in compound **122** and be removable under mild conditions. Desulfurization and removal of P^1 should reveal all methyl groups as well as the triol portion present in compound **125**. It was expected that triol **125** would exist in the hemiacetal form **126** where the C5 hydroxyl group would be internally protected thereby allowing for chemoselective oxidation of C3 and C7 alcohols. Thus, the formation of **126** as the thermodynamically more stable tautomer would provide successful differentiation among the three hydroxyl groups in compound **125**.

The hemiacetal **127** is a ring-chain tautomer of the acyclic form (8*R*)-**114b**. At this stage, removal of the P^2 protecting group would form the muamvatin acyclic precursor (8*R*)-**114a** in its hemiacetal form which would serve the primary objective of this research project (see **Section 2.1**). Thus, P^2 should be robust enough to survive through the synthesis of the fully assembled carbon skeleton **124**, and be removed under

sufficiently mild conditions so as not to interfere with the sensitive functionalities contained in **127**. If this could not be achieved, removal of P^2 after trioxaadamantane formation would be required. Although this would result in a total synthesis of muamvatin, it would preclude studying the origin of this "natural product" (**Scheme 2.1**).

Scheme 2.1 Synthetic strategy towards muamvatin



2.2.1 Synthesis of tris-benzyl ketone 129

The above synthetic strategy towards muamvatin is based on assembly of the full carbon skeleton followed by the oxidation state manipulation of the polyoxygenated carbon chain. In this approach, racemic ketone **9a**[3] was initially used (readily available and easily could be obtained in enantiomerically pure form) in order to establish the chemistry involved along this synthetic route.

Stereoselective aldol coupling of propanal (**86**) with the Ti(IV) enolate formed from ketone **9a** produced aldol adduct **120** as the predominant product (>20:1 dr) in good yield (**Scheme 2.2**). The relative configuration of the newly formed stereogenic centers was assigned by analogy to the previous work in Ward group[9] (see **Figure 1.1**). Previous studies had shown that Ti(IV) mediated aldol reactions of *β*-hydroxy ketones (such as **9a**) have very high 1,3-*syn* enolate diastereoface selectivity and *anti* aldol relative topicity. It was proposed that this high stereoselectivity results from the cyclic Ti(IV) enolate **15a** which makes one face of the enolate much more accessible than the other (**Scheme 2.3**).

Stereoselective reduction of aldol adduct **120** with $NaBH_4$ formed triol **121** (12:1 dr). In the ^1H NMR spectrum of **121**, the large *J* couplings between HC4 and HC5 and between HC5 and HC6 clearly indicated that these protons were axial and thus established the 4,5-*anti* and 5,6-*anti* relative configuration (**Figure 2.3**).

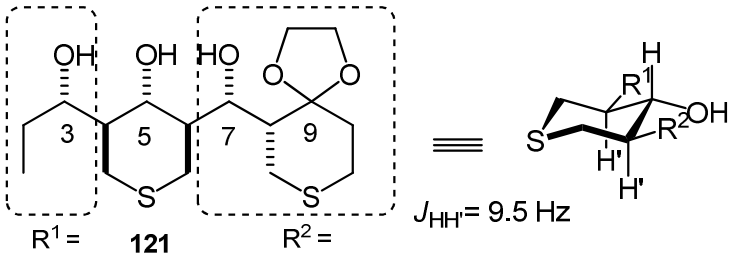
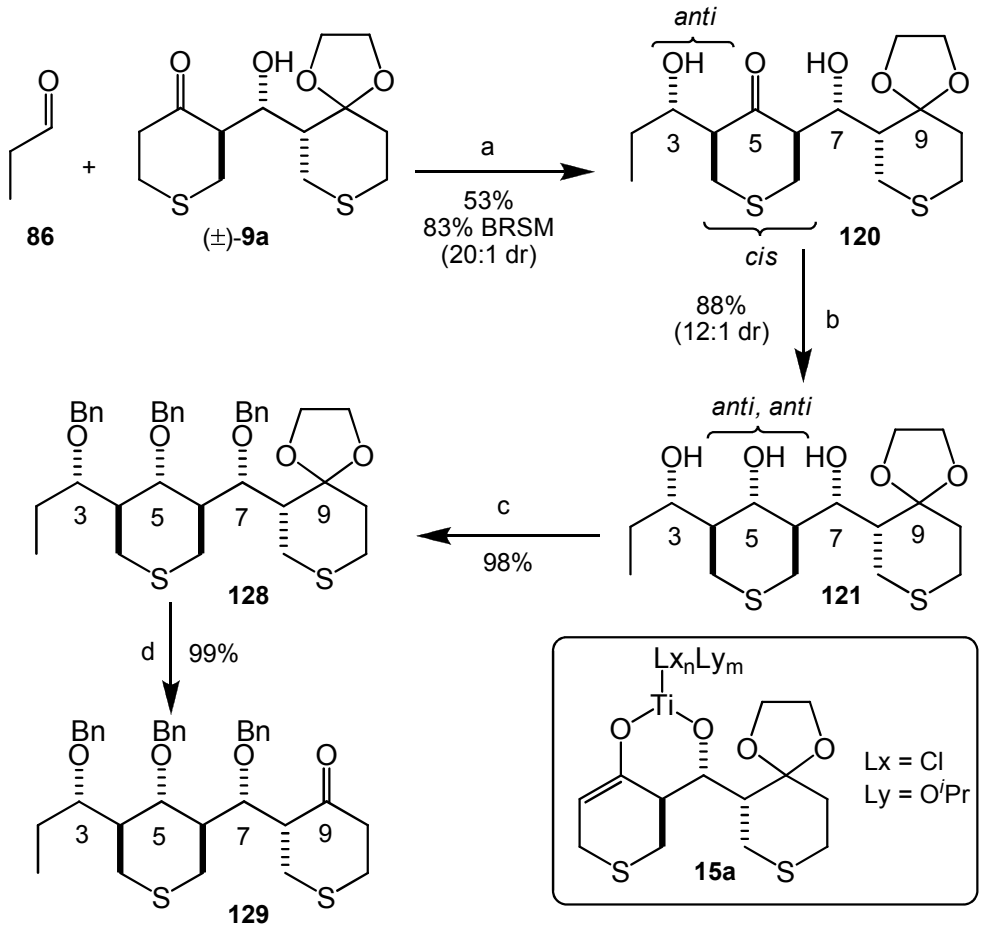


Figure 2.3 Structure elucidation of **121**

Scheme 2.2 Preparation of the tris-benzyl ketone **129**



a) $TiCl_3(O^iPr)$, DIPEA, -78 ºC; b) $NaBH_4$; c) KH, BnBr; d) Amberlyst®, acetone.

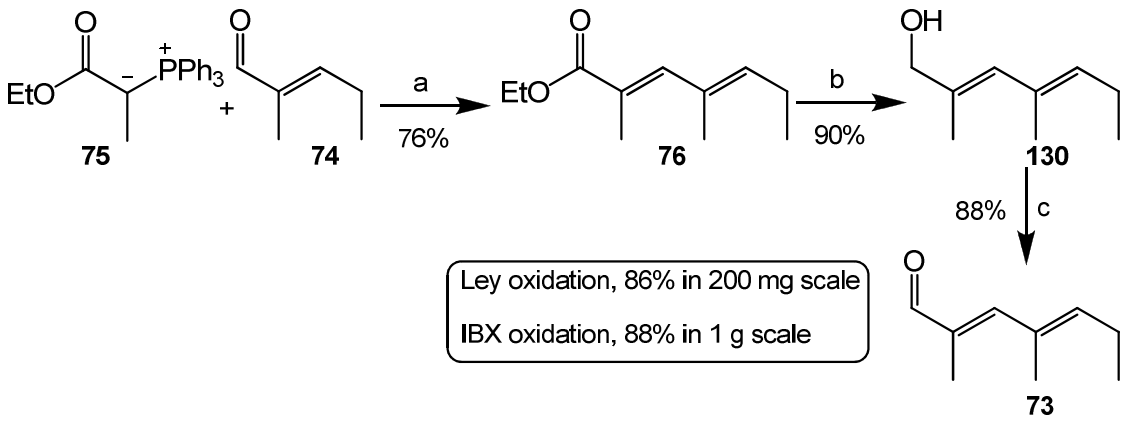
Hydrolysis of the ketal moiety at C9 in **120** would reveal a carbonyl group providing a handle to install the rest of the carbon chain (**Scheme 2.2**). Before that operation, protection of the three hydroxyl groups in triol **121** with a group orthogonal to the ketal was necessary to avoid any unwanted hemiacetal formation by cyclization of the C5-OH onto the C9 ketone moiety. Benzyl (Bn) ethers were chosen due to their robustness to conditions for ketal hydrolysis and having the potential for removal concomitant with the desulfurization process. Alkylation of the triol **121** with benzyl

bromide in the presence of KH formed the tris-benzyl ketal **128** in a good yield. Reaction of **128** with Amberlyst® in acetone gave the desired ketone **129**.

2.2.2 Synthesis of the diene aldehyde 73 and assembly of the full carbon skeleton

As shown previously (**Scheme 2.1**), the planned assembly of the full carbon skeleton of muamvatin required stereoselective aldol reaction between tris-benzyl ketone **129** and diene aldehyde **73**. Aldehyde **73** was prepared as reported previously by Hoffmann et al.[32] except IBX (instead of Pr_4NRuO_4/NMO) was used in the final oxidation step. This modification simplified the procedure and gave comparable yield and purity on larger scale (**Scheme 2.3**).

Scheme 2.3 Preparation of aldehyde **73**



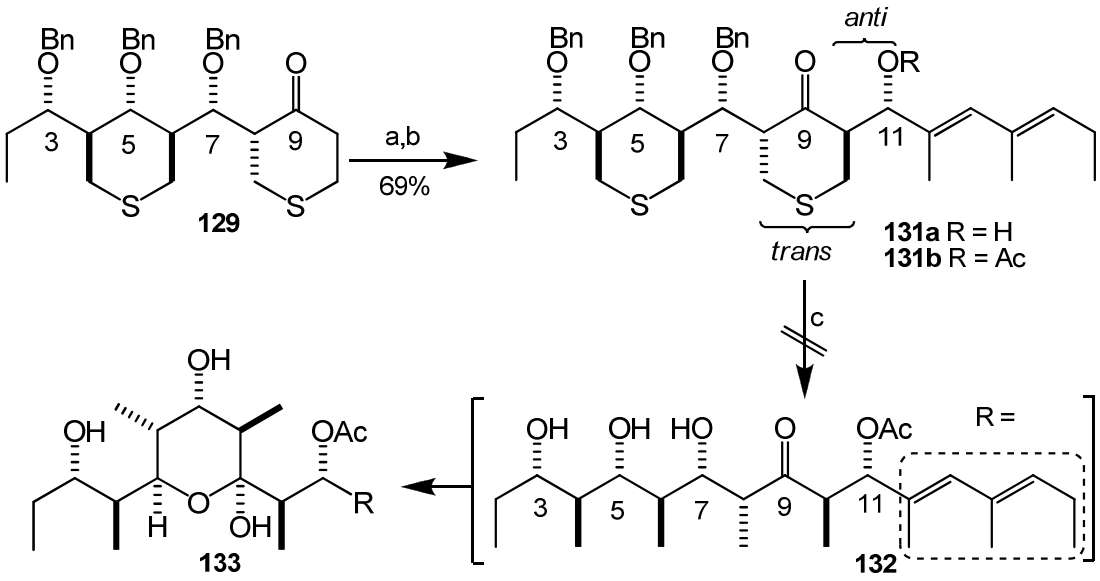
a) THF, reflux; b) $LiAlH_4$, Et_2O; c) IBX, DMSO, rt.

Stereoselective aldol reaction of aldehyde **73** with the enol dicyclohexylborinate derived from ketone **129** gave the adduct **131a** (>20:1 dr) (**Scheme 2.4**). Unfortunately, **131a** could not be separated from unreacted **129**. Reaction of this mixture with Ac_2O and DMAP gave **131b** in good overall yield. The relative configuration of the newly formed stereogenic centers in **131b** was assigned by analogy with the results obtained in the

previously discussed boron mediated aldol reactions of thiopyran ketone similar to **129** (see **Figure 1.2**).[5]

Desulfurization and debenzylation of **131b** should form the acyclic backbone of muamvatin, presumably in its hemiacetal form **133** (**Scheme 2.4**). Not unexpectedly, the diene moiety of the molecule did not survive exposure to Raney Ni. Analysis of the ^{1}H NMR spectrum of the crude products indicated the absence of diene even under conditions of incomplete desulfurization/debenzylation. Thus, either a more chemoselective desulfurization/debenzylation method needed to be developed or the diene portion of the molecule needed to be protected to survive the desulfurization/debenzylation step.

Scheme 2.4 Assembly of the full carbon skeleton of muamvatin



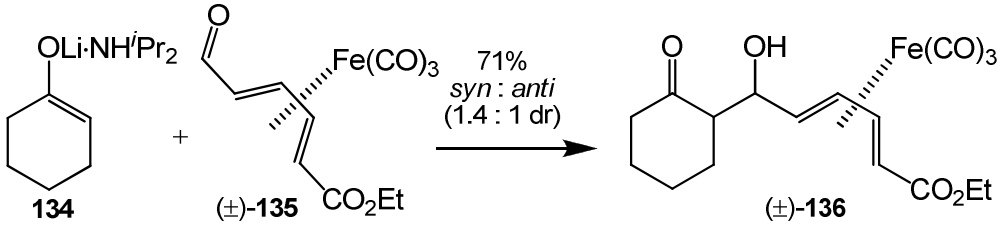
a) $(Chx)_2BCl$, Et_3N, then **73**; b) Ac_2O, DIPEA, DMAP; c) Raney Ni, EtOH.

2.2.3 Revised synthetic strategy

Despite the failed attempt to form the desired hemiacetal **133**, the described methods offered some insight for addressing the problems encountered. The conditions used for desulfurization/debenzylation were not chemoselective enough to avoid reduction of the diene moiety of compound **131**. So, it was hypothesized that protection of the diene portion would enable successful desulfurization/debenzylation of compound **131** without interference from the diene portion.

Looking for a suitable protecting group for the diene portion of the molecule led to tricarbonyliron-diene complexes. Numerous applications of tricarbonyliron-diene complexes in organic synthesis were reported. In particular, tricarbonyl(η4-diene)iron complexes have found flexible applications especially to the regio-, diastereo-,[32,36-38] and enantioselective synthesis of organic compounds[39-42] including biologically active natural products.[43-46] Easy preparation and simple removal of the ironcarbonyl moiety under mild oxidative conditions in the final stage of the synthesis make tricarbonyl(η4-diene)iron complexes versatile compounds.[47,48] Although it was shown that a tricarbonyliron complex of an acyclic, labile diene can protect the diene against reduction and oxidation reactions[48], there are few reports on diastereoselective aldol reactions of (tricarbonyl)iron complex of diene aldehydes.[49,50] For example, the aldol reaction of aldehyde (±)-**135** with lithium enolate **134** gave 71% of two adducts in low diastereoselectivity (1.4:1 dr) (**Scheme 2.5**).[51] With this background, preparation of the tricarbonyl(η4-diene)iron complex of aldehyde **73** was targeted to study its efficiency for the desired purposes.

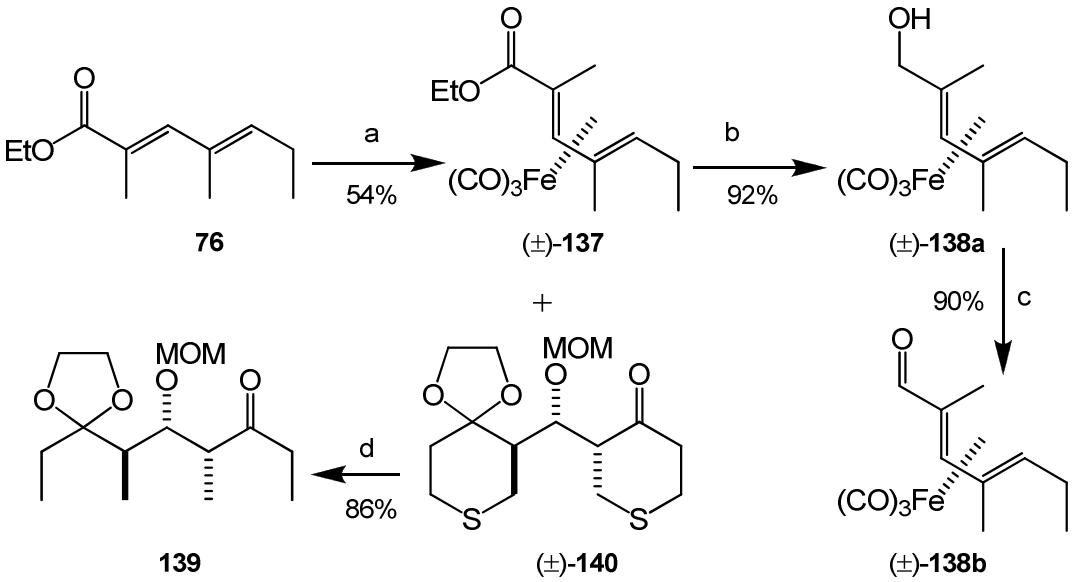
Scheme 2.5 Diastereoselective aldol reaction of aldehyde **135** with enolate **134**



2.2.3.1 Preparation and aldol reactions of the Fe(CO)$_3$ protected diene aldehyde 138b

Known methods were adapted to prepare the desired aldehyde (±)-**138b** (**Scheme 2.6**). Reaction of diene ester **76** with $Fe_2(CO)_9$ formed complex (±)-**137** in moderate yield.[46,48] Reduction of ester (±)-**137** with DIBAL-H gave the corresponding alcohol (±)-**138a** with minimal loss of the ironcarbonyl moiety.[52,53] IBX oxidation of (±)-**138a** provided aldehyde (±)-**138b** in good yield. The choice of solvent was found to be crucial for the oxidation step. Standard solvents for the IBX mediated oxidation (such as acetonitrile or DMSO) resulted in either a very slow rate or partial removal of the $Fe(CO)_3$ moiety. Using THF as a co-solvent with DMSO resulted in a reasonable rate of oxididation with minimal deprotection of the iron complex. The efficacy of this diene protection was tested by desulfurization of **140** in the presence of (±)-**137** which gave desulfurized ketone **139** without any decomposition of (±)-**137** (**Scheme 2.6**).

Scheme 2.6 Preparation of diene Iron complex (±)**-138b**



a) $Fe_2(CO)_9$, Benzene, reflux; b) DIBAL-H, THF, -78 ºC; c) IBX, (THF:DMSO 1:2); d) Raney Ni, EtOH, reflux.

Complexation of the achiral diene aldehyde **73** with $Fe(CO)_3$ results in the chiral aldehyde (±)-**138b**. Thus, the presence of the tricarbonyliron moiety generates a new stereogenic element. An aldol reaction of aldehyde (±)-**138b** with a chiral ketone (i.e., tris-benzyl ketone **129**) can produce up to eight possible adduct diastereomers. According to the multiplicativity rule,[20,54] the stereoselectivity of aldol reactions between chiral fragments can be factorized into three stereocontrol elements: *i*) enolate face selectivity, *ii*) aldehyde face selectivity, and *iii*) aldol relative topicity. A highly stereoselective aldol reaction has all three of these stereocontrol elements highly biased (see **Section 1.1.2**).

Previous studies in the Ward group, have shown that the enolate diastereoface selectivity of closely related tetrapropionate synthons, such as **9**, can be manipulated to favor 3,5-*syn* or 3,5-*anti* aldol adducts by having the C1′-OH free or protected, respectively.[4] The aldol relative topicity can also be manipulated to be highly *syn* or *anti*

selective by using different enolates (i.e., boron or Ti(IV) "ate") (see **Section 1.1.2**).[5] Lastly, numerous examples of nucleophilic addition to 2,4-dienals bearing tricarbonyl(η4-diene)iron complexes showed that the population of *s-cis* and *s-trans* conformers dictated the diastereoface selectivity (the addition of the nucleophile selectively occurred *exo* to the (tricarbonyl)iron moiety) (**Figure 2.4**).[38] The distribution of the two conformers (*s-cis* vs. *s-trans*) depends on several features such as the diene substituents, the nature of the nucleophile, temperature, and presence or absence of a Lewis acid.

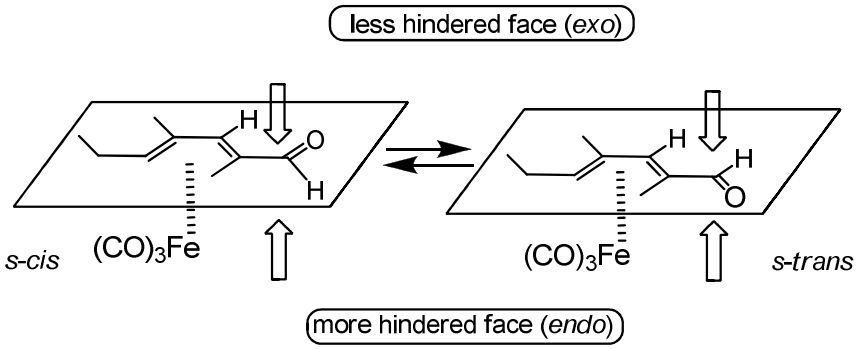
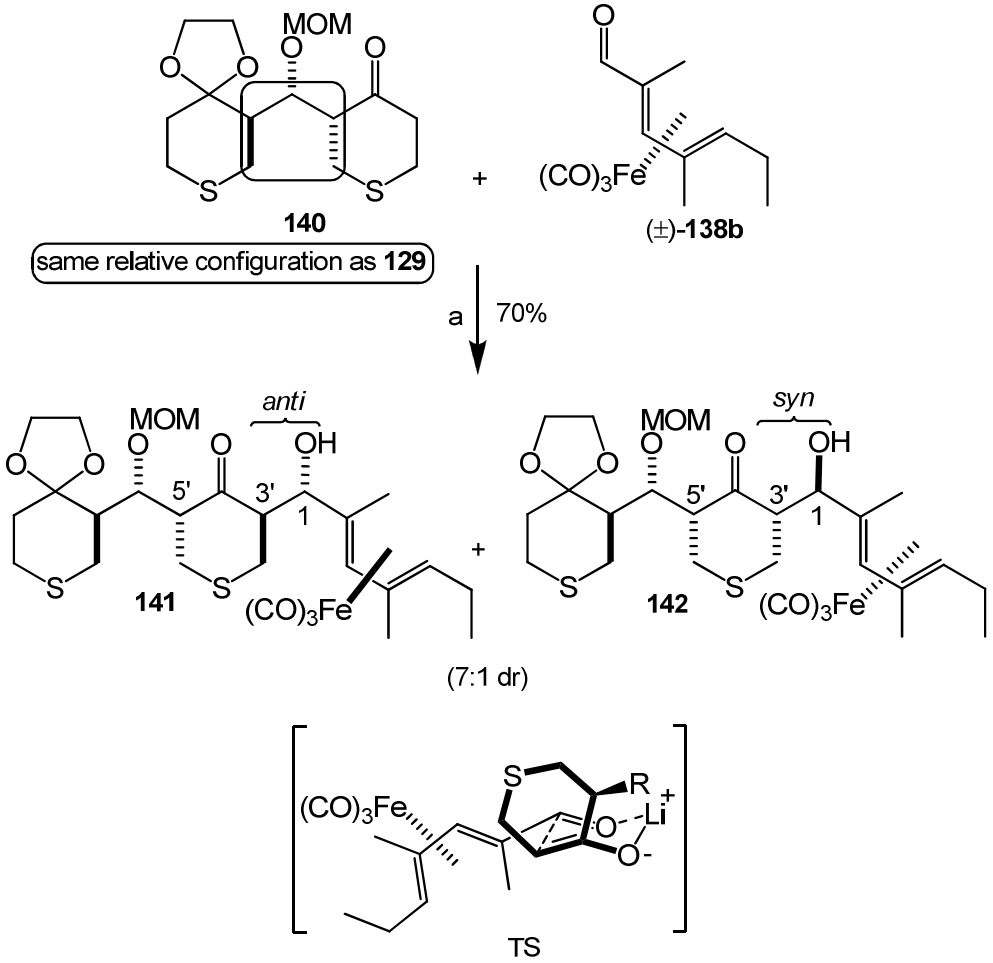


Figure 2.4 The diastereo-face selectivity of aldehyde (±)-**138b**

To test the reactivity and selectivity of aldehyde (±)-**138b**, a model aldol reaction with ketone **140** (a closely related analogue to tris-benzyl ketone **129**) was conducted (**Scheme 2.7**). Surprisingly, none of the common enolates derived by reaction of **140** with $(Chx)_2BCl/Et_3N$, $TiCl_4/Et_3N$, $TiCl_3(O^iPr)/Et_3N$ or LDA produced any aldol adduct, under various conditions. The reactivity of aldehyde **73** was apparently diminished drastically in its complexed form with $Fe(CO)_3$. However, using the 'amine free' Li enolate of ketone **140,** generated via direct enolization by ^{t}BuLi, gave a 70% yield of two aldol adducts in a 7:1 ratio (based on ^{1}H NMR of the crude reaction mixture). The relative configurations of the major and minor aldol adducts **141** and **142** were determined from

their X-ray crystal structures (**Figure 2.5**). Accordingly, both adducts were formed with the same aldehyde diastereoface selectivity, presumably by addition to the less hindered face of the *s-trans* conformer (see **Figure 2.4**). The major adduct had the desired 3',5'-*trans*-1,3'-*anti* relative configuration which is the out come of the favored transition state shown in **Scheme 2.7**.

Scheme 2.7 Model study on aldol reaction of aldehyde **(±)-138**



a) ^{t}BuLi, -78 ºC then (±)-**138b**

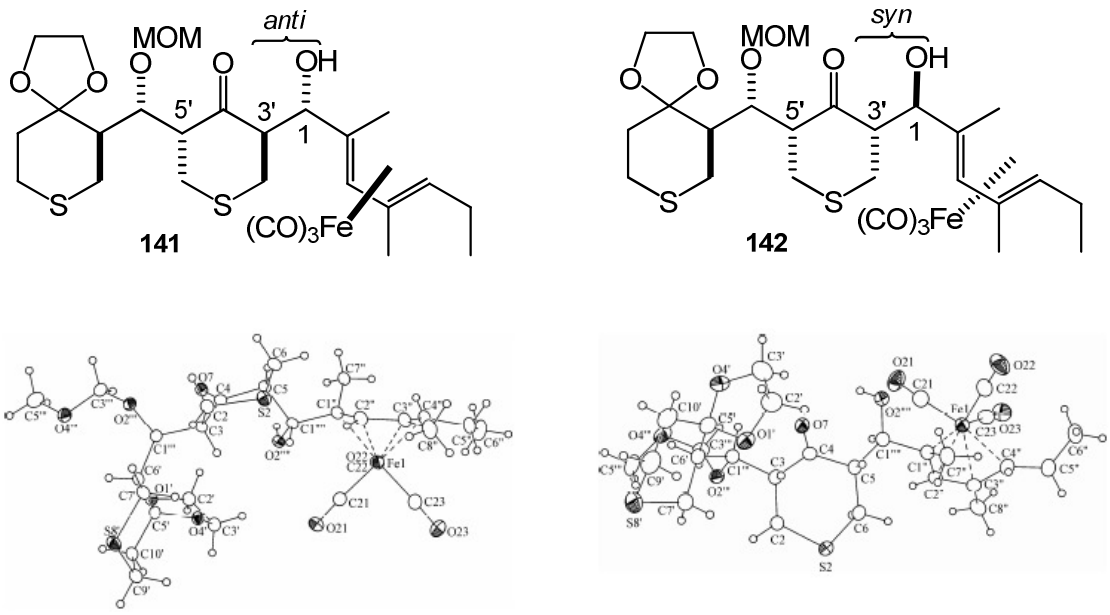
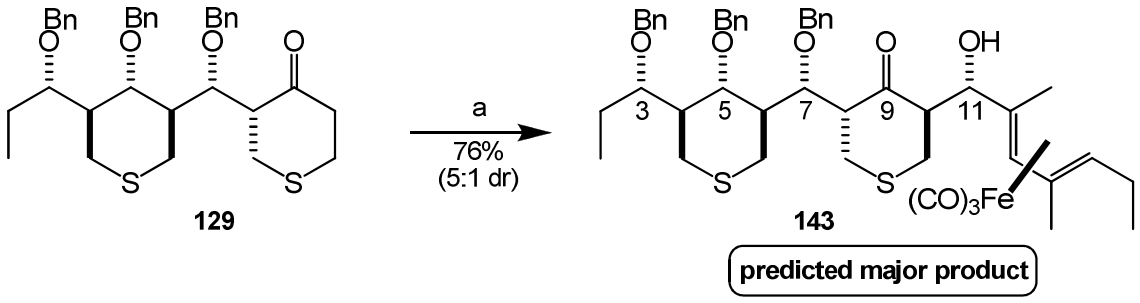


Figure 2.5 ORTEP representations for **141** and **142**

2.2.3.2 Preparation of the full carbon skeleton of muamvatin using aldehyde (±)-138b and its deprotection studies

Applying the above method to the aldol reaction of aldehyde (±)-**138b** with ketone **129** gave an inseparable 5:1 mixture of two diastereomeric aldol adducts **143** in good yield (**Scheme 2.8**). The configuration of the major product was assumed to be 8-10-*anti*-10,11-*anti* in analogy to the major adduct **141** obtained in the model study (**Scheme 2.7**). Obtaining aldol adduct **143** in reasonable yield provided an avenue for further investigation because the diene moiety of the fully assembled carbon skeleton was protected from reduction under Raney Ni conditions needed for desulfurization/debenzylation.

Scheme 2.8 Assembly of the full carbon skeleton using aldehyde **(±)-138b**

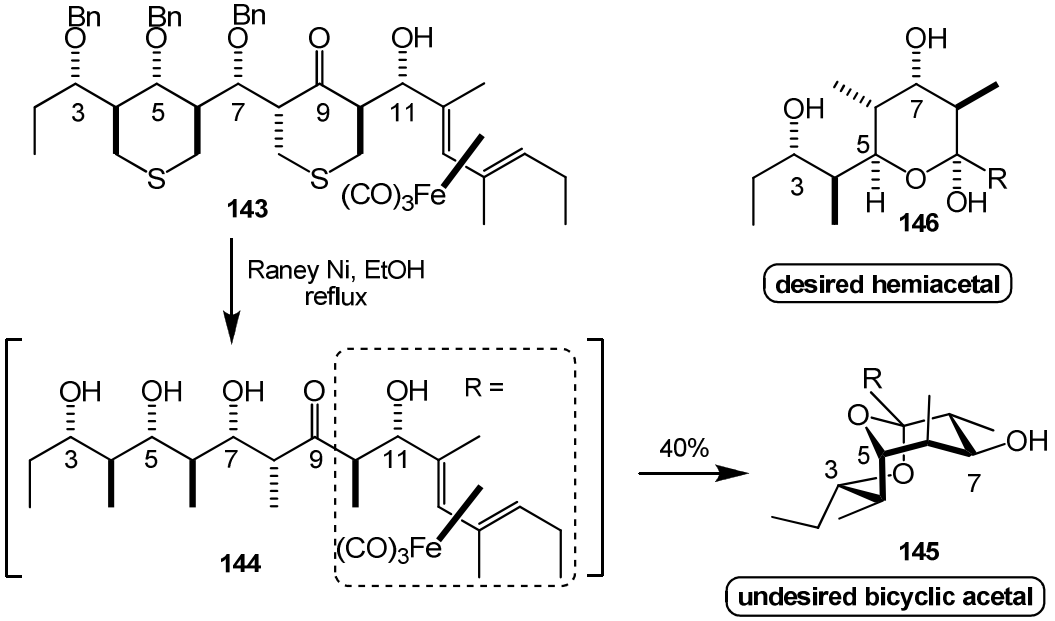


a) ^{t}BuLi, -78 ºC then (±)-**138b**

In order to effectively utilize **143**, the C11-OH needed to be orthogonally protected with respect to the benzyl groups at C3, C5 and C7 positions so as to allow chemoselective oxidation of the OH groups at C3 and C7. Fortuitously, the C11-OH showed very high resistance towards protection even with small protecting groups such as acetate. This observation implied that the iron carbonyl moiety acted as a protecting group for both the diene and the C11-OH. In the ideal case, debenzylation and desulfurization of **143** should form the desired hemiacetal **146** (**Scheme 2.9**), ready for further oxidation state manipulation with the C11-OH group protected by the adjacent $Fe(CO)_3$ group.

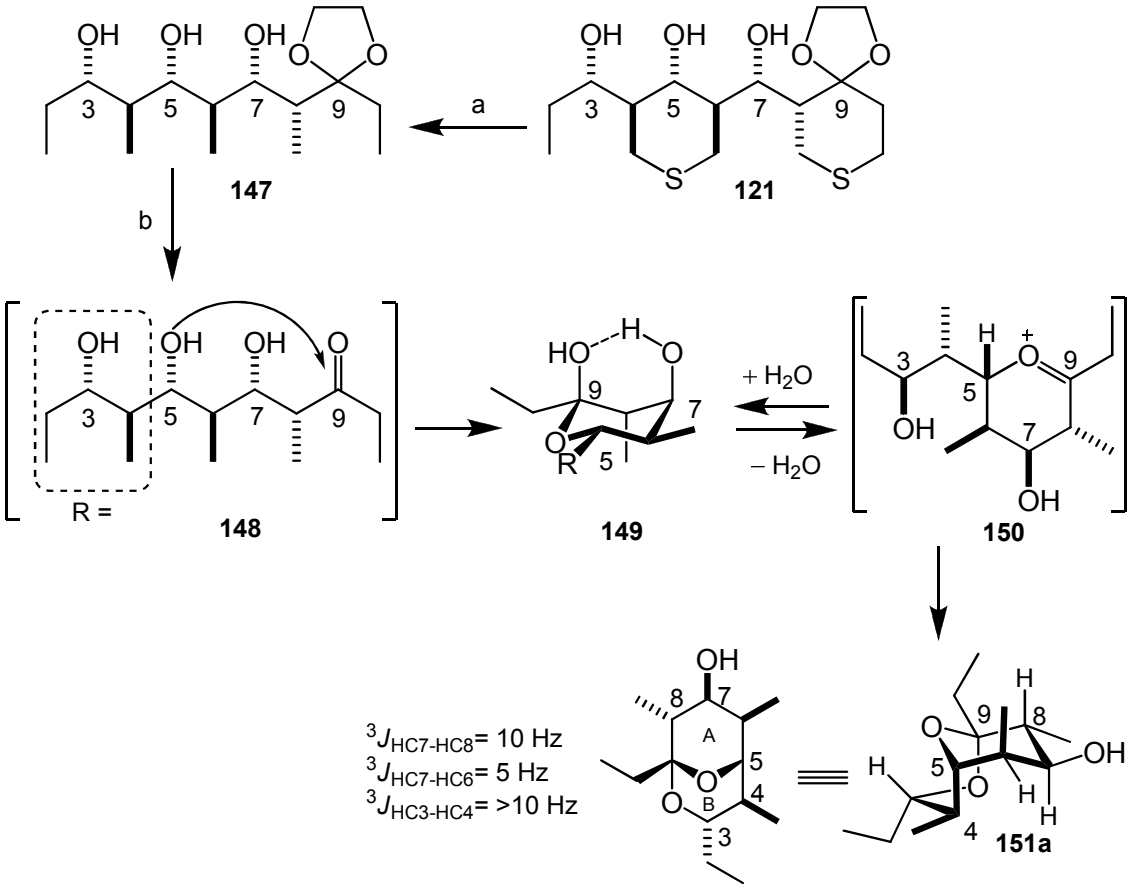
Treatment of **143** with Raney Ni successfully desulfurized the fully assembled carbon skeleton revealing all methyl groups at C4, C6, C8, and C10 (**Scheme 2.9**). Concomitantly, hydrogenolysis of benzyl ethers also occurred revealing the hydroxyl groups at C3, C5 and C7 positions without affecting the diene portion of the molecule. Unfortunately, instead of the desired hemiacetal **146**, the only product isolated from the reaction mixture was the bicyclic acetal **145**.

Scheme 2.9 Desulfurization and debenzylation of **143**



The undesired result of the reaction of **143** with Raney Ni required a careful analysis of the bicyclic ring system in product **145** to understand the problem in hand. Perhaps, conditions could be found to hydrolyze the bicyclic ring system **145** to the desired hemiacetal **146**. In this regard, the model compound **151a** was prepared by Raney Ni desulfurization of the triol ketal **121** followed by treatment with aqueous acid (**Scheme 2.10**). A plausible expectation from this reaction was to obtain the desired hemiacetal **149** that has a favorable anomeric effect at C9, a stabilizing hydrogen bond between the C3-OH and C9-OH, and most of the substituents on the six-membered ring in equatorial orientations. Instead, the reaction mixture showed only bicyclic ketal **151a**. The chair conformation of ring A in bicyclic acetal **151a** was established based on the large (10 Hz) $^{3}J_{HH}$ between HC-7 and HC-8 and the medium (5 Hz) $^{3}J_{HH}$ between HC-7 and HC-6 observed in the ^{1}H NMR spectrum. The boat conformation for ring B was suggested by the large (10 Hz) $^{3}J_{HH}$ between HC-3 and HC-4.

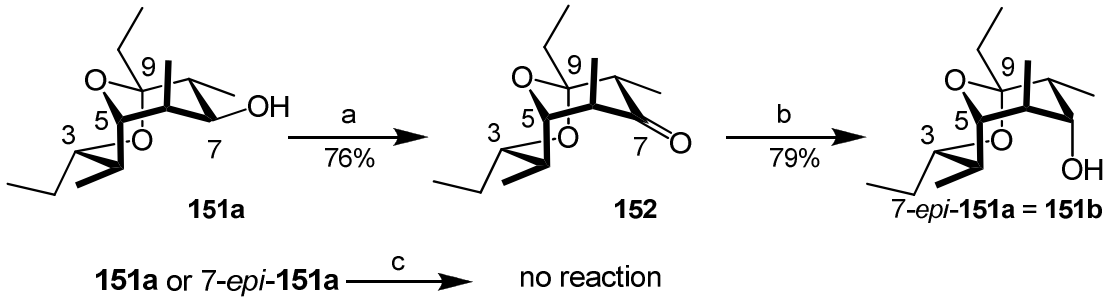
Scheme 2.10 Preparation of the bicyclic model system **151a**



a) Raney Ni, EtOH, reflux; b) HCl, H_2O/THF, rt.

The stability of the bicyclic acetal **151a** was tested by exposure to different acidic conditions (**Scheme 2.11**); however, only starting material was harvested from the reaction mixtures. In hope of destabilizing the bicyclic ketal **151a**, the configuration of hydroxyl group at C7 was inverted by oxidation followed by reduction to give **151b**. However, as with **151a**, exposure of **151b** to various acidic conditions failed to produce detectable amounts of hemiacetal 7-epi-**149**. Unfortunately, the synthetic strategy outlined in **Scheme 2.1** failed.

Scheme 2.11 Preparation and stability of 7-*epi*-**151a**



a) IBX, THF/DMSO; b) $NaBH_4$, MeOH; c) H^+, H_2O/THF under various conditions.

2.2.4 Summary and conclusion

So far, the fully assembled carbon skeleton of muamvatin has been completed twice (having the diene portion protected and unprotected) via application of the thiopyran route to polypropionates. Although muamvatin was not synthesized by these routes, they do show the effectiveness of this strategy for achieving fast and stereoselective assembly of polypropionate motifs. It was also shown that the $Fe(CO)_3$ moiety can act as an efficient protecting group for diene systems during reductive desulfurization conditions (i.e., Raney Ni). However, the inherent tendency of the trihydroxy ketone moiety of **144** to spontaneously form bicyclic acetal **145** could not be suppressed and this route was abandoned.

2.3 Synthesis of muamvatin, part 2: the 'acyclic' route

As previously shown (**Scheme 2.1**), obtaining intermediate **126** is crucial to the planned total synthesis of muamvatin. Unfortunately, the tendency of ketone **144** to spontaneously form the bicyclic acetal **145** instead of the desired hemiacetal **146** resulted in a dead end for that route (**Scheme 2.9**). Although formation of the desired hemiacetal

150 from the bicyclic system **151a** also failed (**Scheme 2.10**), modifications of the initial strategy (**Scheme 2.1**) offered some potential to solve the encountered problem.

Considering the preparation of the linear precursor (8*R*)-**114a** from ketone triol **153**, the configurations of the three stereogenic centers at C3, C7, and C8 are variable (**Figure 2.6**). This is because the C3 and C5 stereogenic centers are not present in muamvatin and the configuration at C8 is readily epimerizable and can be established under thermodynamic control. In the previous route, the tris-hydroxy ketone **155** had the substituents at C3, C5 and C8 with a *syn* relative configuration which ultimately led to spontaneous formation of the bicyclic compound **156**. The configurations of these three stereogenic centers presumably play an important role in the facility of this cyclization of the starting triol ketone **155**. Considering the triol ketone **154** as a simpler model of **153** (**Figure 2.6**), eight diastereomers are possible by varying the relative configurations of the stereogenic centers at C3, C7, and C8.

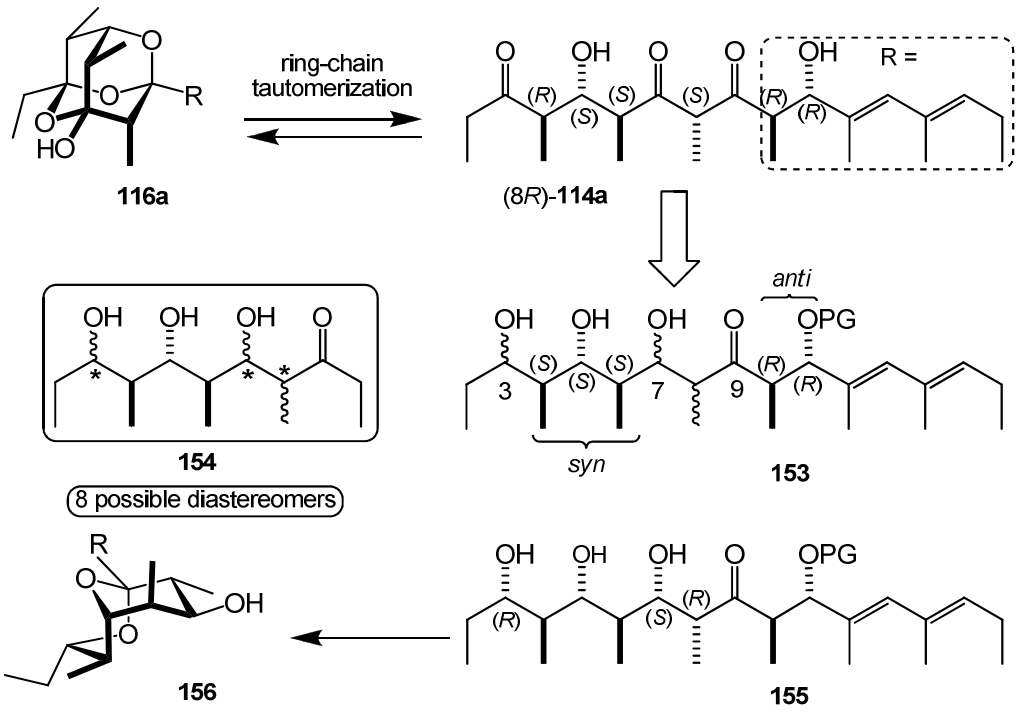


Figure 2.6 Looking back to the previous strategy

Simple molecular mechanics calculations, employing Spartan software,* on the eight bicyclic acetals **151a-h** suggested that the ground state energies for the eight possible diastereomers are very different (**Figure 2.7**). Consistent with the experimental results, the (3*R*,7*S*,8*R*) diastereomer, **151a**, was by far the most stable diastereomer. Hoffmann et al. observed formation of **151b**[33] (the second most stable bicyclic acetal) from (3*S*,7*S*,8*R*)-**154** under acidic conditions. However, Paterson et al. did not observe any sign of closely related bicyclic acetal **151d** in their approach to the total synthesis of muamvatin.[31] Based on these observations, it was hypothesized that the higher the ground state energy of the bicyclic system, the lower the facility of its undesired formation. Out of eight diastereomeric forms, the two diastereomers **151f** (3*S*,7*R*,8*S*) and **151h**

* All calculations were performed using the software Spartan '08 V 1.2.0 for Microsoft Windows from Wave function, Inc. The calculations represent the ground state energy of the most stable conformer as determined using Molecular Mechanics/MMFF (Merck Molecular Force Field) model.

(3*S*,7*S*,8*S*) showed the highest ground state energies. Based on their relative ease of preparation, the linear precursor (3*S*,7*R*,8*S*)-**154** was targeted for synthesis in a modification of the previous strategy.

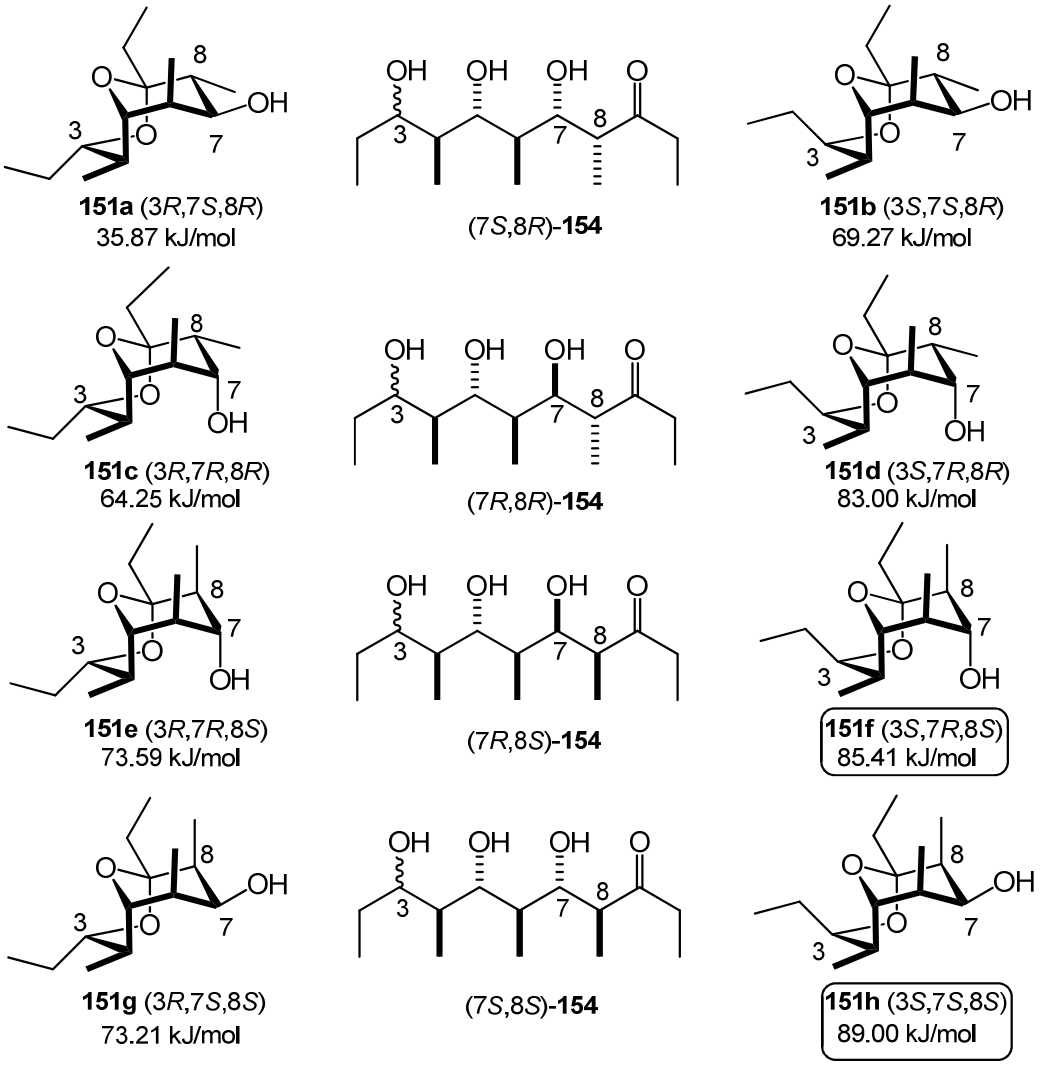


Figure 2.7 All possible diastereomeric forms of **151** in bicyclic form

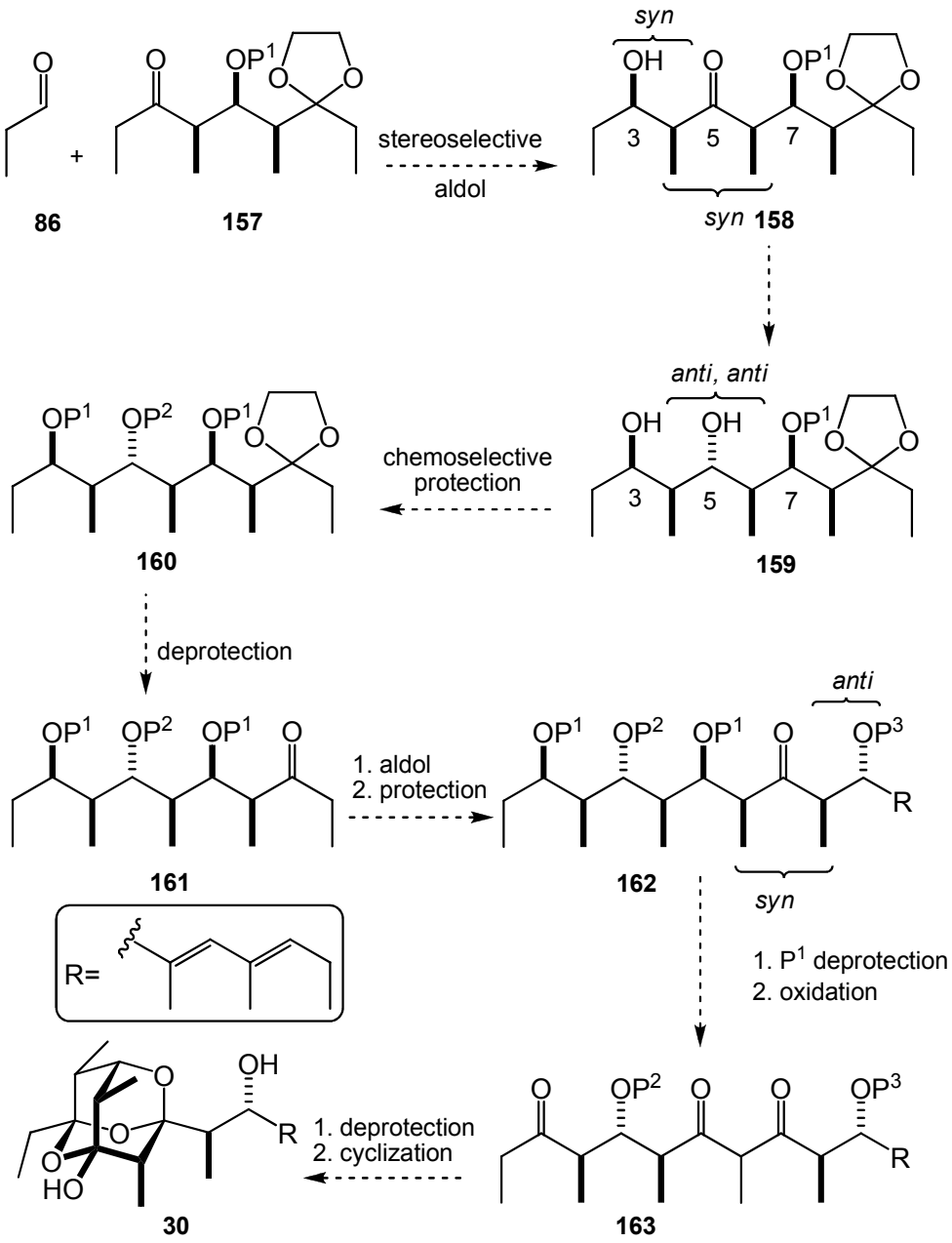
2.3.1 Revised synthetic analysis

The assembly of the full carbon skeleton was envisioned through stereoselective aldol reactions of the two achiral aldehydes **86** and **73** with enantiomerically pure ketone

157 (**Scheme 2.12**). In this approach, using the acyclic ketone **157** avoids complication of chemoselectivity during the desulfurization process with respect to competitive reduction of the diene moiety as observed in the previous route (see **Section 2.2.2**). To form the triol ketone (3*S*,7*R*,8*S*)-**154**, stereoselective aldol reaction of ketone **157** with propanal (**86**) followed by stereoselective reduction of the C5 carbonyl in adduct **158** and protecting group manipulation would provide the ketone **161**. Finally, a stereoselective aldol reaction of ketone **161** with diene aldehyde **73** would produce the complete muamvatin carbon skeleton.

Proper manipulation of protecting groups is essential for the success of this synthetic plan. Not only must the P^1 and P^2 protecting groups be orthogonal to each other but also they need to survive the conditions required for deprotection of the C9 ketal moiety. Selective removal of the P^1 protecting groups in **162** followed by oxidation of the hydroxyl groups at C3 and C7 would provide the fully functionalized carbon backbone **161**. Finally, the P^2 and P^3 protecting groups in compound **161** must be removed under mild conditions so as not to affect the sensitive functionalities needed to form the trioxaadamantane ring system (**Scheme 2.12**). If necessary, the P^3 protecting group could be removed after formation of the trioxaadamantane ring system to avoid any destructive interference from other functionalities on the molecule.

Scheme 2.12 Revised synthetic strategy



2.3.2 Model studies on diastereoselective aldol reaction of the acyclic ketone (-)-164

As discussed in the previous section, the carbon skeleton **162** is envisioned to result from two stereoselective aldol reactions between the two achiral aldehydes **86** and **73** with the masked hydroxydiketone **157** (**Scheme 2.12**). The aldol reaction of ketone

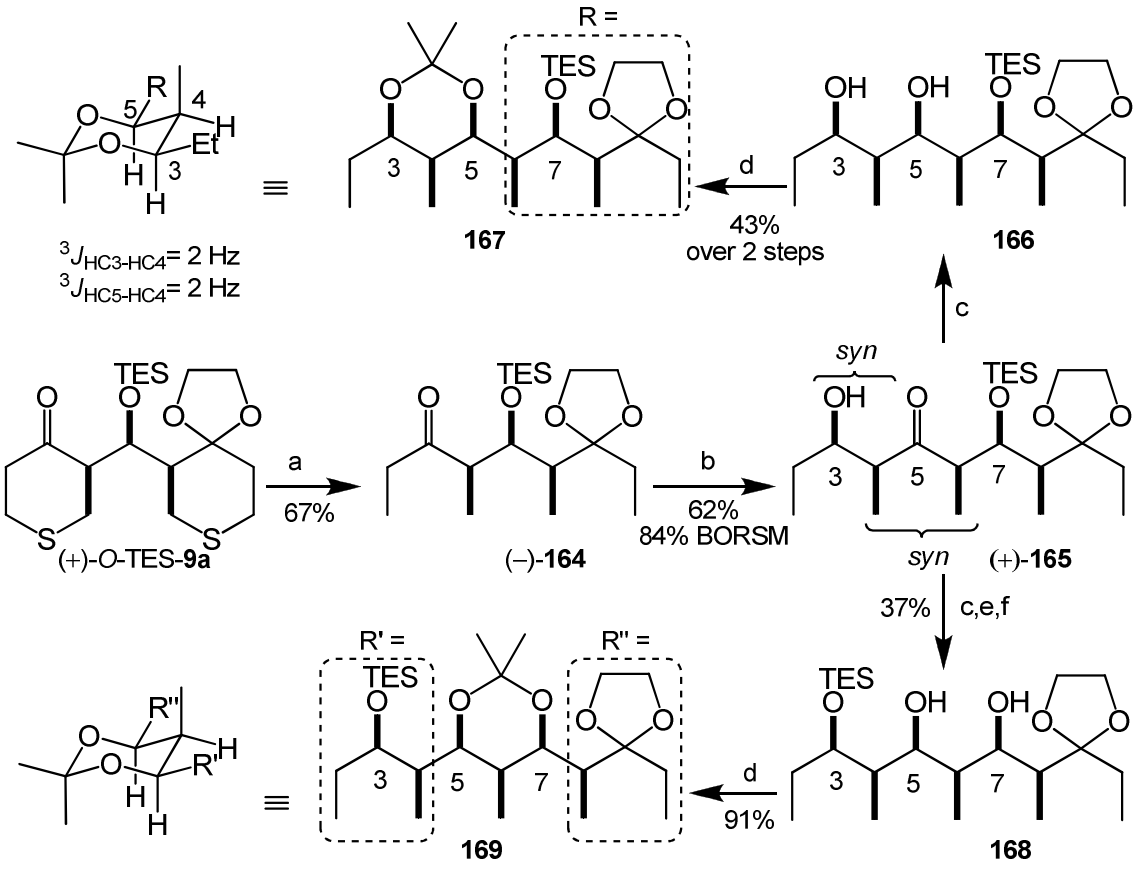
157 with propanal (**86**) must proceed with selective addition to the (*Z*)-enolate *re* face with *syn* aldol relative topicity to form the desired adduct **159**. On the other hand, the aldol reaction of diene aldehyde **73** with ketone **161** must proceed by selective addition to the (*E*)-enolate *re* face with *anti* relative topicity to give the desired adduct **162**. At this stage, it was considered prudent to establish the conditions needed to obtain the desired stereoselectivities in these aldol reactions using model compounds.

2.3.2.1 The syn-syn aldol reaction of ketone (-)-164 with propanal (86)

The readily available (+)-*O*-TES-**9a**[5] (ref. **Figure 2.2**) was transformed to ketone (-)-**164** (**Scheme 2.13**). With ketone (-)-**164** in hand, the *syn* selective aldol reaction with propanal (**86**) could be attempted. Literature precedent suggests that the (*Z*)-boron enolates, prepared by reaction of a 2-alkyl ethyl ketones with 9-BBNOTf and $^{i}Pr_2EtN$, react with aldehydes to give adducts with 1,3-*syn* methyl groups and *syn* aldol relative topicity.[55,56] The (*Z*)-boron enolate of ketone (-)-**164** was prepared by adapting the conditions used in previous research by Paterson et al.[55] and treated with propanal (**86**) to give aldol adduct (+)-**165** in 62% yield and high diastereoselectivity (>20:1 dr by ^{1}H NMR of the crude product). In order to establish the relative configuration of newly formed stereogenic centers, the carbonyl group at C5 was reduced with $LiAlH_4$ and the resulting diol was protected as the acetonide **167** (**Scheme 2.13**). The ^{13}C NMR spectrum of **167** showed methyl signals at 20 and 30 ppm establishing the 3,5-*syn* relative configuration in **167**.[57] The key 3,4-*syn* relative configuration in compound **167** (i.e., from *syn* aldol relative topicity) was established based on the small coupling constants ($^{3}J_{HH}$= 2 Hz) observed between HC3-HC4 and HC4-HC5 in the ^{1}H NMR spectrum of **167**.

In order to establish the relative configuration at C4 and C6 (i.e., from the enolate diastereoface selectivity in the aldol reaction), the regioisomeric acetonide **169** was prepared as outlined in **Scheme 2.13**. The ^{13}C NMR spectrum of **169** showed the two acetonide methyl groups at ca. 20 and 30 ppm establishing a 5,7-*syn* relative configuration[57] and, considering the already established 6,7-*syn* and 4,5-*syn* relative configurations, indicated the presence of a 4,6-*syn* relative configuration in **169**. Thus, the adduct (+)-**165** results from an aldol reaction with *syn* relative topicity to *re* diastereoface of the (*Z*)-enolate of (-)-**164**, as was required by the synthetic plan.

Scheme 2.13 Stereoselective aldol reaction of (-)-**164** with propanal (**86**)



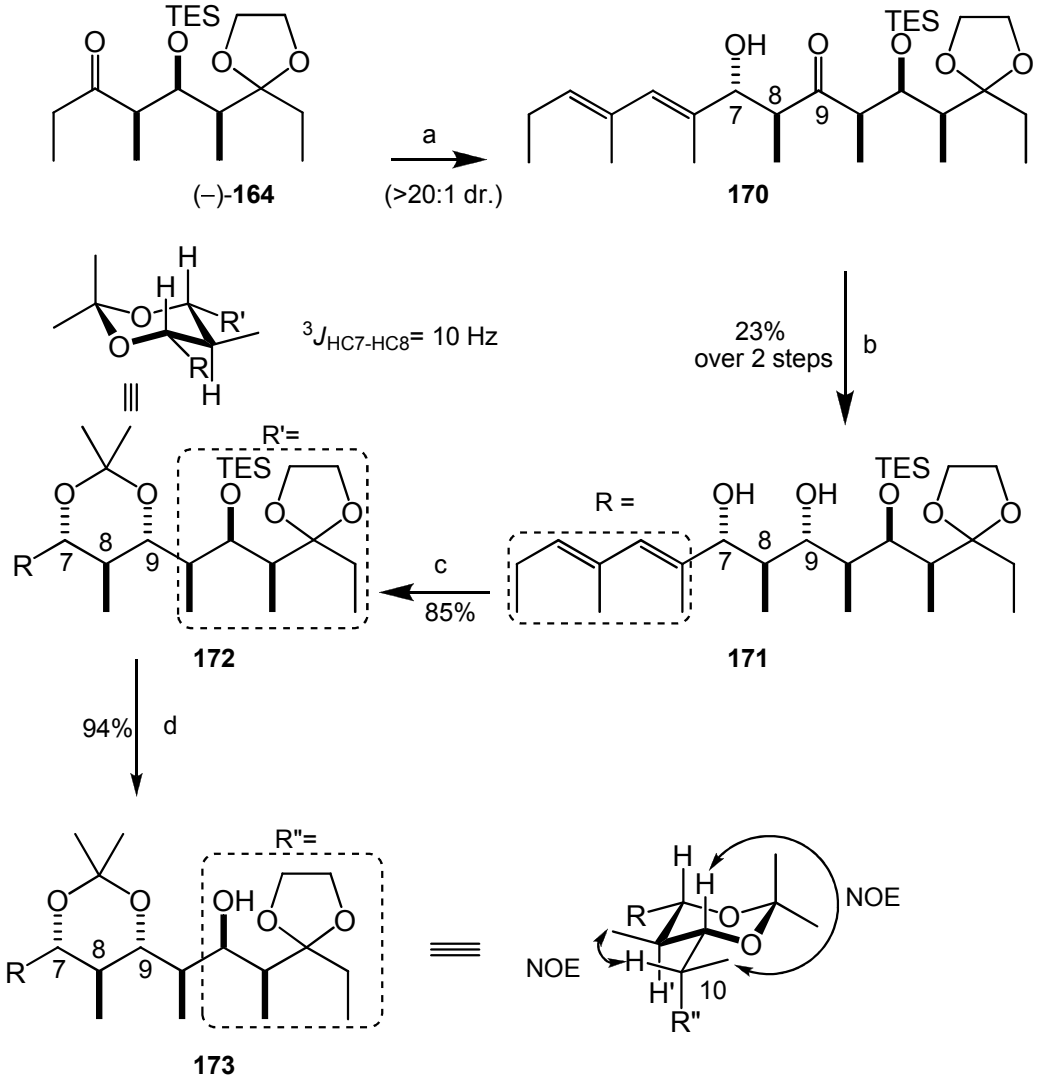
a) Raney Ni, EtOH, Reflux; b) 9-BBNOTf, Et_3N, -78 ºC then **86**; c) $LiAlH_4$; d) 3,3-dimethoxypropane, PTSA; e) TBAF; f) Et_3SiOTf, 2,6-lutidine,0 ºC.

2.3.2.2 The model syn-anti aldol reaction of ketone (-)-164 with diene aldehyde 73

As mentioned previously (**Section 2.3.1**), the carbon skeleton of muamvatin was envisioned to result from stereoselective aldol reaction of enantiomerically pure ketone **161** with diene aldehyde **73**. The desired aldol adduct **162** would result from addition to the *re* face of (*E*)-enolate of **162** with *anti* aldol relative topicity. It is known that (*E*)-boron enolates prepared by reaction of 2-alkyl ethyl ketones with $(Chx)_2BCl$ and Et_3N reacts with various aldehydes to give the desired selectivity.[58-60] In order to test whether the above analysis was valid, ketone (-)-**164** (a closely related analogue to ketone **161**) was treated with $(Chx)_2BCl$ and Et_3N followed by addition of diene aldehyde **73** to give the aldol adduct **170**. Stereoselective reduction of **172** with DIBAL-H followed by acetonide protection of the resulting diol **171** (>20:1 dr) gave **172** (**Scheme 2.14**). The ^{13}C NMR spectrum of **172** showed acetonide methyl groups at ca. 20 and 30 ppm establishing a 7,9-*syn* relative configuration.[57] The *anti* relative configuration between hydroxyl group at C7 and methyl group at C8 was established based on the magnitude of coupling constants for the vicinal hydrogens at C7 and C8 ($^3J_{HH}$= 10 Hz) observed in the ^1H NMR spectrum of **172**. The relative configuration of the methyl groups at C8 and C10 was determined to be *syn* based on NOE experiments on alcohol **173** prepared by treatment of **172** with TBAF. A positive NOE was detected on CH_3-C8 upon irradiation of the C10 methine hydrogen (**Scheme 2.14**). Similarly, irradiation of the C10 methyl group gave a positive NOE on the C9 hydrogen. Together, these NMR studies confirmed the relative configuration of the model aldol adduct **170** as shown in **Scheme 2.14**.

At this stage, with the viability of the two key stereoselective aldol reactions confirmed, a plausible path to form the carbon skeleton of muamvatin was in hand.

Scheme 2.14 Aldol reaction of **73** with the (*E*)-boron enolate of ketone (-)-**164**



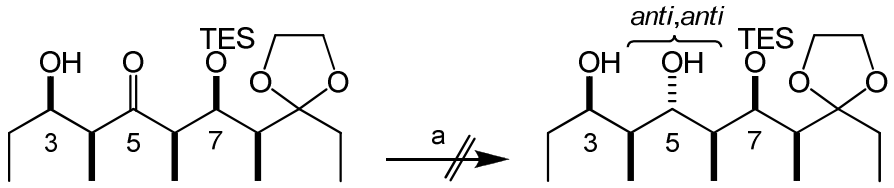
a) $(Chx)_2BCl$, Et_3N; b) DIBAL-H, -78ºC; c) 3,3-dimethoxypropane, PTSA; c) TBAF, THF, RT.

2.3.3 Stereoselective reduction of ketone (+)-165 and preparation of the tris-allyl ketone 188

With the desired aldol adduct (+)-**165** in hand, stereoselective reduction of the C5 ketone was attempted. Despite numerous attempts using various known methods for directed hydride delivery, such as $NaBH_4$, $Zn(BH_3)_2$, or $NaBH(OAc)_3$,[61-63] no sign of

desired diol **174** was observed and the starting ketone (+)-**165** was recovered from the reaction mixture (**Scheme 2.15**).

Scheme 2.15 Attempts on stereoselective reduction of ketone (+)-**165**

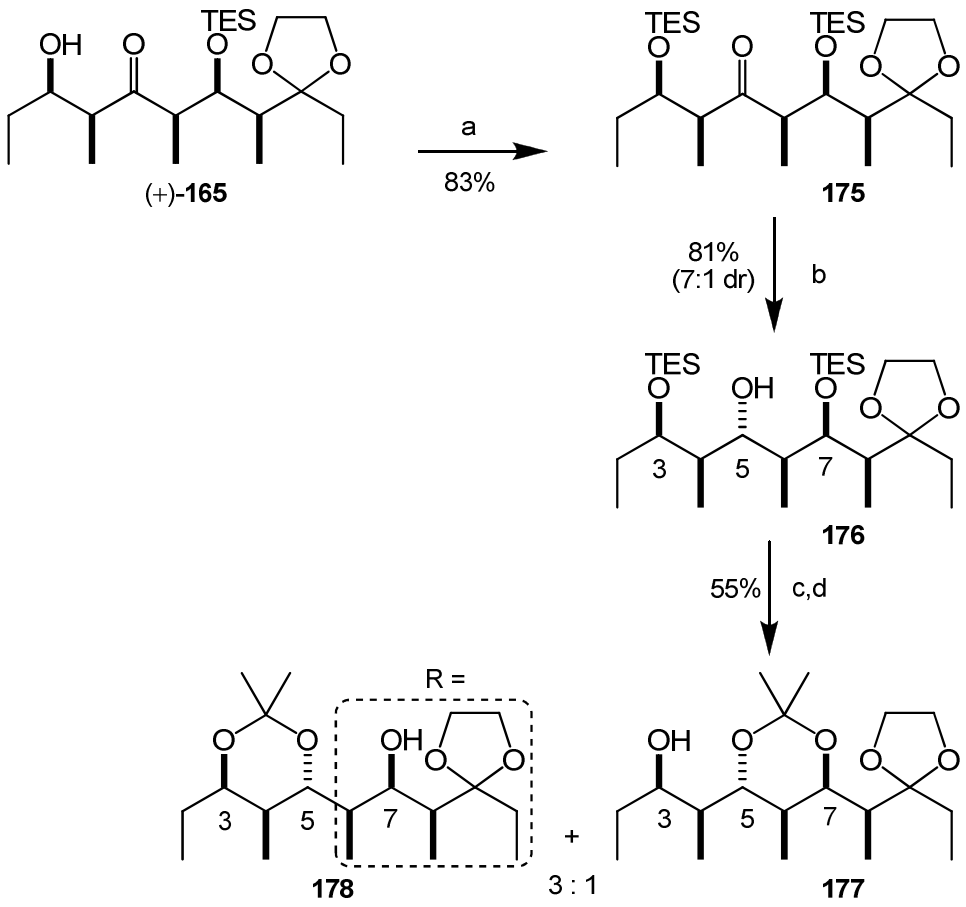


(+)-**165** **174**

a) $NaBH_4$, $Zn(BH_4)_2$, or $NaBH(OAc)_3$ under various conditions.

In an alternative approach, the C3 hydroxy group of (+)-**165** was protected as its triethylsilyl ether to form **175**. Reaction of ketone **175** with super hydride ($LiEt_3BH$) formed the desired alcohol **176** in good diastereoselectivity (7:1 dr) (**Scheme 2.16**). After hydrolysis of the silyl ethers, the major diastereomer was transformed into an inseparable 3:1 mixture of acetonides **177** and **178**. Analysis of the ^{13}C NMR spectrum for this mixture showed a pair of acetonide methyl groups at ca. 25 ppm for both isomers strongly suggesting a 3,5-anti-5,7-*anti* relative configuration in the precursor **176**.[57] Thus, protecting the C3 hydroxyl group in aldol adduct (+)-**165** not only facilitated the stereoselective reduction of ketone **175** but also provided an opportunity for orthogonal protection of the C5 hydroxy group in compound **176** as previously discussed (**Section 2.3.1**, **Scheme 2.12**).

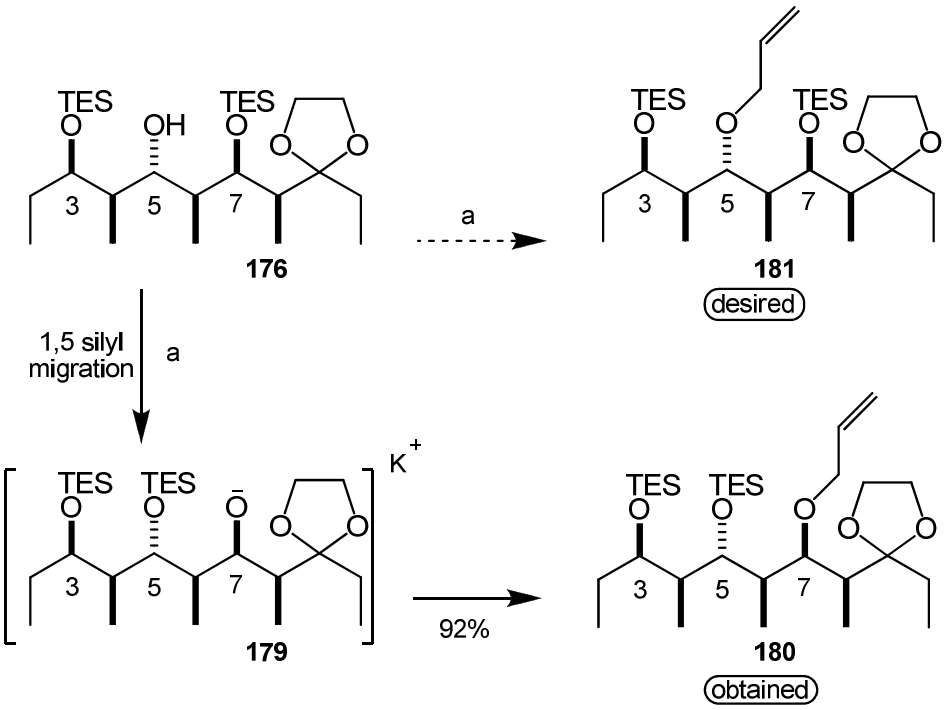
Scheme 2.16 Stereoselective reduction of (+)-**165**



a) Et_3SiCl, imidazole, DMF; b) $LiEt_3BH$, 0 ºC to RT; c) TBAF; d) 3,3-dimethoxypropane, PTSA.

Allyl ether was chosen as an appropriate protecting group. Reaction of **176** with KHMDS followed by addition of allylbromide gave the allyl protected compound **180** as the only product isolated instead of the desired **181** (**Scheme 2.17**). Presumably the presence of two triethylsilyl ether groups at C3 and C7 prevented the alkylation of the alkoxide group at C5 and a 1,5 silyl migration became the favored pathway. Failing to selectively protect the C5-OH group in compound **176**, required a few changes in the synthetic plan to address this issue (**Scheme 2.18**).

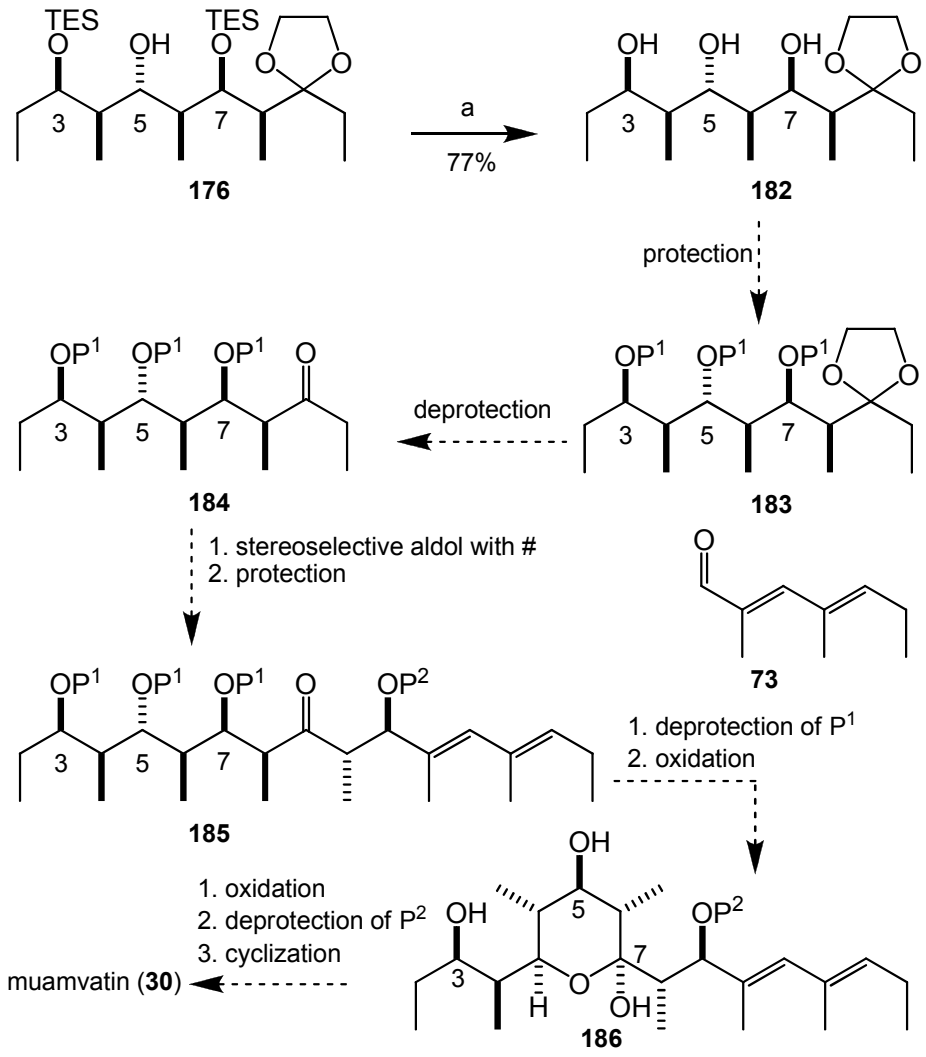
Scheme 2.17 1,5-Silyl migration and allyl protection of **176**



a) KHMDS/DMPU then allyl bromide.

The two silyl protecting groups in **176** can be removed to make triol **182** (**Scheme 2.17**). Protection of the triol **182** with a group orthogonal to the ketal will allow formation of ketone **184**. Stereoselective aldol reaction of **184** with aldehyde **73** will form aldol adduct **185** that can be protected with a group different from P^1. The ability to remove the P^1 protecting groups under mild condition is crucial in order to form the desired hemiacetal **186**. Formation of the key hemiacetal **186** internally protects the C5-OH group and allows chemoselective oxidation of the hydroxyl groups at C3 and C7 thereby leading to the fully functionalized carbon skeleton of muamvatin. Finally, removal of the P^2 protecting group under mild conditions would provide the desired precursor to study the formation of the trioxaadamantane ring system and complete the synthesis of muamvatin (**Scheme 2.17**).

Scheme 2.18 Alternative avenue in the synthetic strategy

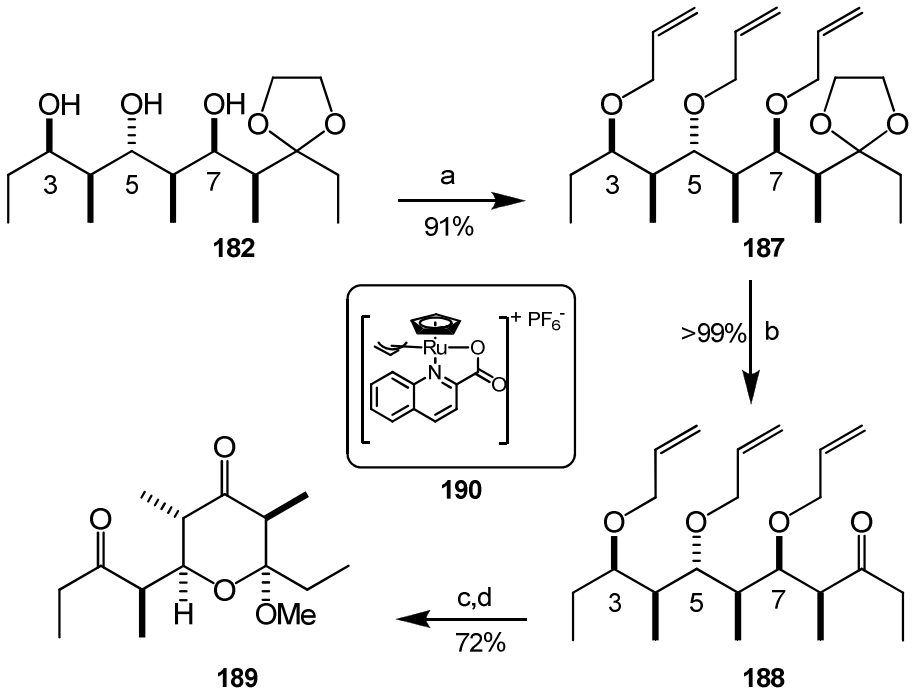


a) TBAF, THF, RT.

As mentioned previously, the choice of the P^1 protecting group is essential to the success of this approach. Recently, a new catalyst was introduced by Kitamura et al. for efficient removal of allyl ethers under mild conditions.[64] Very low loading (<1 mol%) of the Ru(IV) catalyst **190** in a protic solvent was sufficient to remove different types of allyl ethers at ambient temperature. More importantly, catalyst **190** showed high chemoselectivity towards allyl groups without any destructive affect on alkynes, alkenes,

or aromatic rings.[65] To test the efficiency of this catalyst, tris-allyl ketal **187** was prepared which then upon exposure to $FeCl_3 \cdot 6H_2O$ formed ketone **188** quantitatively (**Scheme 2.19**). Ketone **188** is the tris-allyl derivative of (3*S*,7*R*,8*S*)-**154** (**Figure 2.7**). At this stage, it was worthwhile to examine the hypothesis discussed previously (**Section 2.3**) and test the susceptibility of (3*S*,7*R*,8*S*)-**154** towards formation of the bicyclic compound **151f** (**Scheme 2.19**). The allyl groups in ketone **188** were removed under very mild conditions (2 mol% of catalyst **190** at 30 ºC) and the product was immediately subjected to IBX oxidation to give diketone **189** in good yield. This experiment demonstrated that formation of a bicyclic acetal was not especially facile for (3*S*,7*R*,8*S*)-**154** and that chemoselective oxidation via the hemiacetal was possible for this diastereomer.

Scheme 2.19 Preparation of ketone **188**

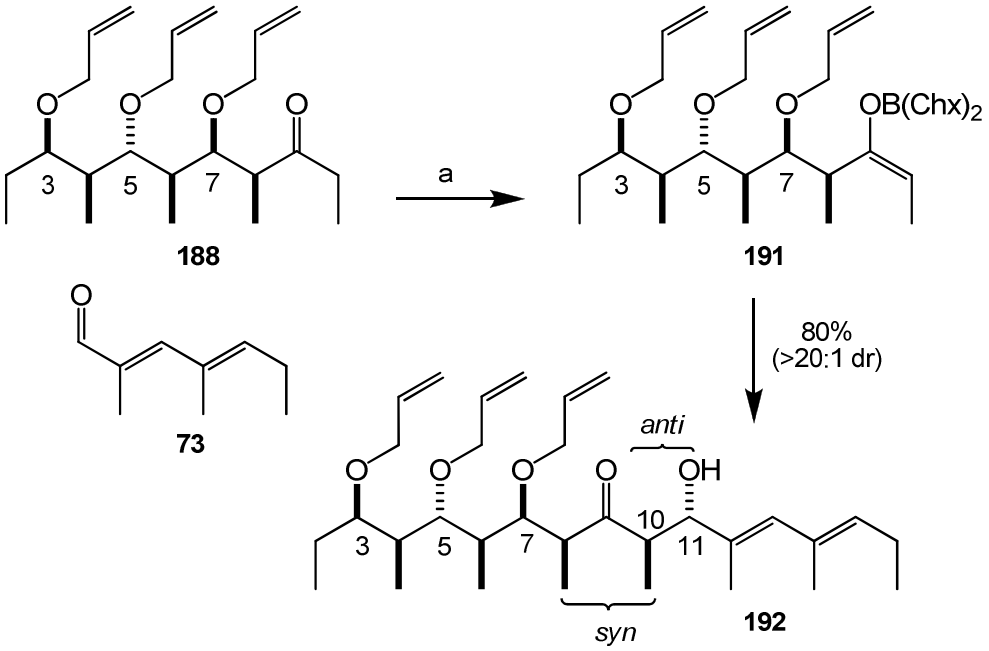


a) KHMDS, DMPU then allyl bromide, -78 ºC to rt; b) $FeCl_3 \cdot 6H_2O$; c) **190**, (2mol%), MeOH, 30 ºC; d) IBX, DMSO/THF.

2.3.4 Assembly of the full carbon skeleton

With ketone **188** and aldehyde **73** in hand, an aldol reaction to couple these reactants could be attempted. Treatment of ketone **188** with $(Chx)_2BCl$ and Et_3N gave the putative (*E*)-enol borinate **191** that after addition of diene aldehyde **73** gratifyingly gave a 81% yield of predominantly one aldol adduct **192** (>20:1 dr, judged by ^1H NMR spectroscopy) (**Scheme 2.20**). It was assumed that **192** had the indicated relative configuration, based on the results obtained in the model reaction (**Scheme 2.14**).

Scheme 2.20 Stereoselective aldol reaction of ketone **188** with aldehyde **73**



a) $B(Chx)_2Cl$, Et_3N then **73**.

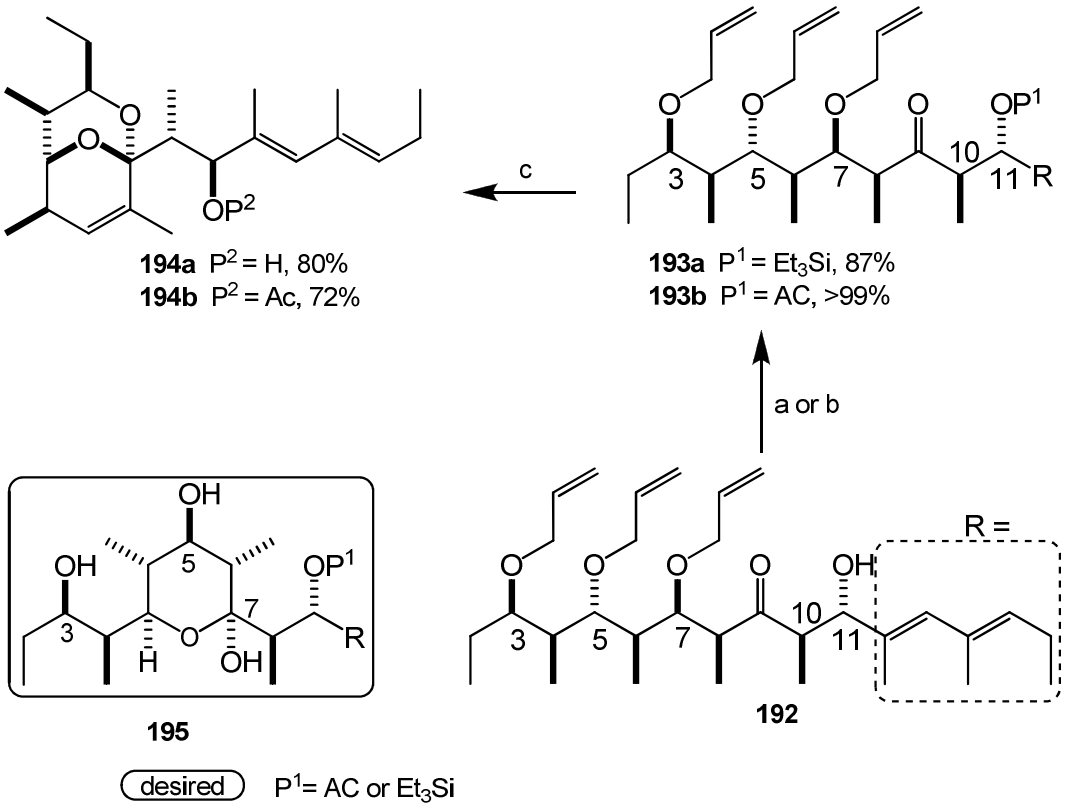
2.3.5 Deallylation studies on the fully assembled carbon skeleton 192

With aldol adduct **192** in hand, the oxidation of both hydroxyl groups at C3 and C7 could be tried. In order to manipulate the oxidation state of the fully assembled carbon

skeleton **192**, protection of the hydroxyl group at C11 and deprotection of the hydroxyl groups at C3, C5, and C7 were attempted.

The C11-OH group was first protected as the triethylsilyl ether **193a** (**Scheme 2.21**). Exposure of ketone **193a** to a catalytic amount of Ru(IV) complex **190** in methanol gave bicyclic compound **194a** as the only product. Deprotection of triethylsilyl ether moiety as well as elimination of the allyl ether at C7 suggested that **193a** was very sensitive to the deallylation conditions. Subsequently, the C11-OH group was protected as the acetate **193b**. However, subjecting **193b** to the deallylation conditions, gave bicyclic acetal **194b** (**Scheme 2.21**). Despite extensive experimentation on the deallylation step, the only fully deprotected products obtained were the bicyclic acetals **194a** and **194b**. It was uncertain whether the elimination reaction leading to **194a/194b** occurred before the deallylation of the C7-OH (i.e., elimination of H-O-allyl) or after deallylation (i.e., elimination of H-OH). It was decided to conduct the deallylation-cyclization process in a stepwise manner. Thus, protection of the C9 ketone moiety would prevent the formation of a hemiacetal and disfavor elimination without affecting the deallylation process. The desired protecting group must survive the deallylation process and should be removable under mild condition without affecting the resulting triol. The *O*-trimethylsilyl-cyanohydrin (*O*-TMS cyanohydrin) was chosen as a suitable protecting group (**Scheme 2.22**).

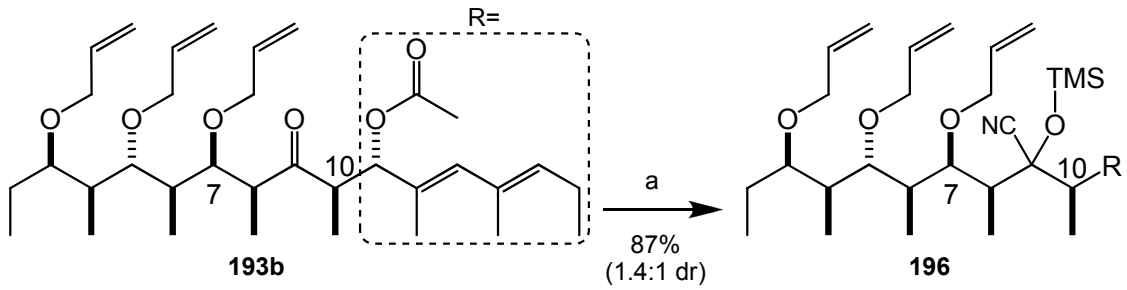
Scheme 2.21 Deallylation of the fully assembled carbon skeleton



a) Et_3SiOTf, 2,6-lutidine; b) AC_2O, DMAP, DIPEA; c) **190**, (2mol%), MeOH, 30 ºC.

A number of methodologies have been developed over the years to protect ketones as their *O*-trimethylsilyl-cyanohydrin. Some of these methods are based on using TMSCN with Lewis acids such as $Yb(CN)_3$,[66] $Yb(OTf)_3$,[67] $Eu(fod)_3$,[68] $MgAlCO_3$,[69] while others rely on nucleophilic addition of cyanide to carbonyl moieties such as KCN, 18-crown-6/Me_3SiCN,[70] and Me_3SiCN/KCN/ZnI_2[71]. Of these methods, nucleophilic addition of cyanide ion using the 18-crown-6·KCN catalyst developed by Evans et al.[70] followed by *in situ* protection of the resulting cyanohydrin as its trimethylsilyl ether was promising and with optimization gave a reasonable yield of **196** as a 1.4:1 mixture of diastereomers (**Scheme 2.22**).

Scheme 2.22 Protection of the ketone moiety in **193b**

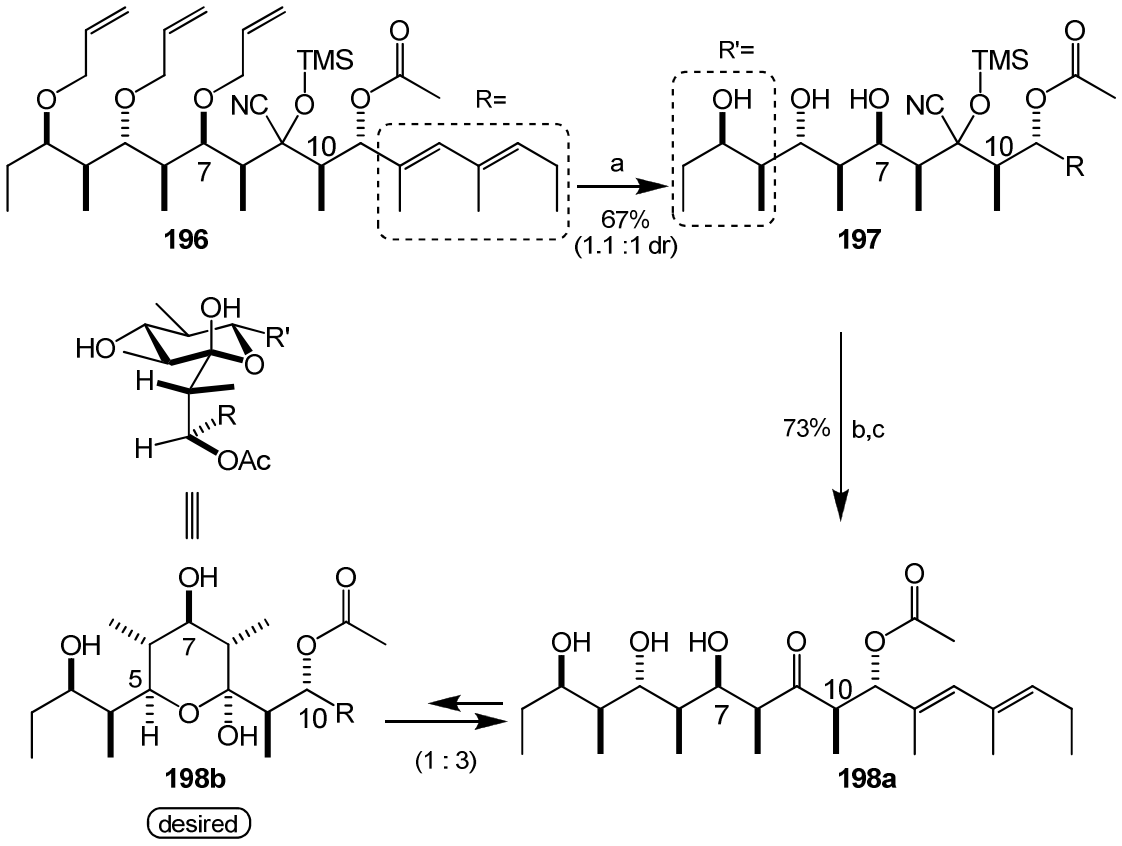


a) TMSCN, 18-crown-6·KCN, rt.

Successful deallylation of **196** formed a diastereomeric mixture of triol **198** with no sign of formation of **194b** (**Scheme 2.23**). Removal of the *O*-trimethylsilyl-cyanohydrin under mild conditions revealed the ketone **198a**. Surprisingly, the desired hemiacetal **198b** was not thermodynamically favored (**198a**:**198b**, 3:1). Thus, the resulting mixture was not synthetically useful for chemoselective oxidation.

Not being able to get the hemiacetal **198b** as the more thermodynamically stable tautomer was very disappointing at this stage. Conformational analysis of the desired hemiacetal **198b** revealed a strong steric interaction between the dienyl group and the oxygen atom of the hemiacetal ring system. This interaction presumably favors triol ketone **198a** (opened form) over **198b** (closed form) despite the latter having all possible substituents in equatorial orientation (**Scheme 2.23**).

Scheme 2.23 Formation of the ketone triol **198**



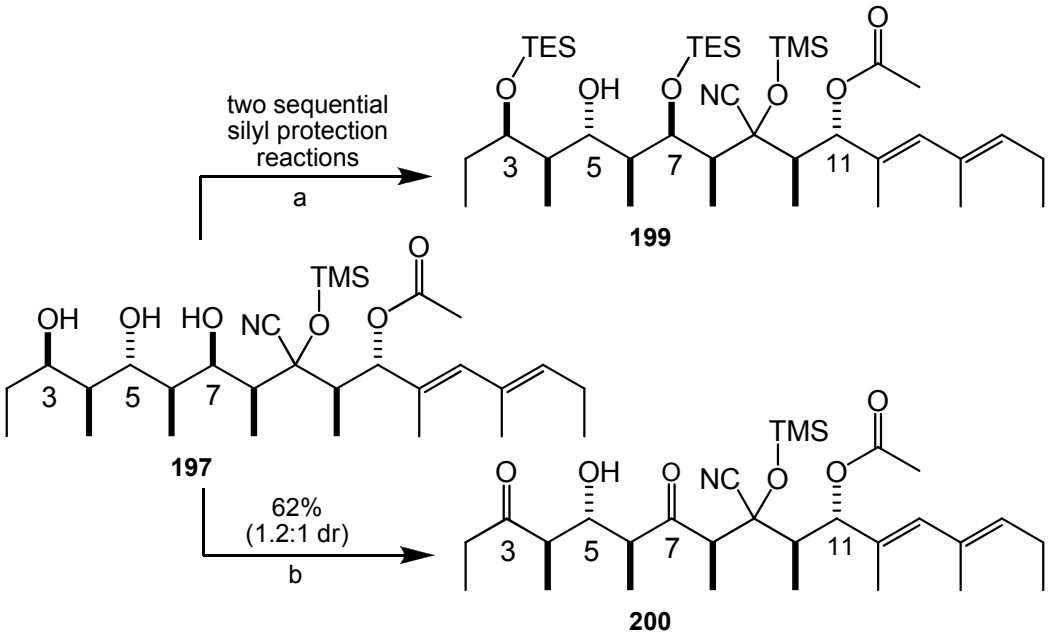
a) **190**, (2mol%), MeOH, 30 ºC; b) HF·Py/Py, H_2O (cat.); c) H_2O/MeOH, reflux.

2.3.6 Chemoselective oxidation and the end game

Comparison of the triol ketone **198a** with compound **114b** (see **Figure 2.1**) revealed the only difference between the two structures was the oxidation state of hydroxyl groups at C3 and C7. Unfortunately, achieving that transformation was complicated because the internal protection of C5-OH via hemiacetal ring formation was not favored (**Scheme 2.23**). Experiments aimed at assessing possible protection schemes, showed a very clear differential reactivity among the three hydroxyl groups in the diastereomeric mixture of triol **197** (**Scheme 2.24**). Stepwise triethylsilyl ether protection of **197** gave alcohol **199** indicating highly selective reaction of the C3 and then the C7

hydroxyl groups in preference to the C5 hydroxyl. This remarkable result suggested a possible direct solution to the desired transformation (chemoselective oxidation of C3, and C7 over C5).

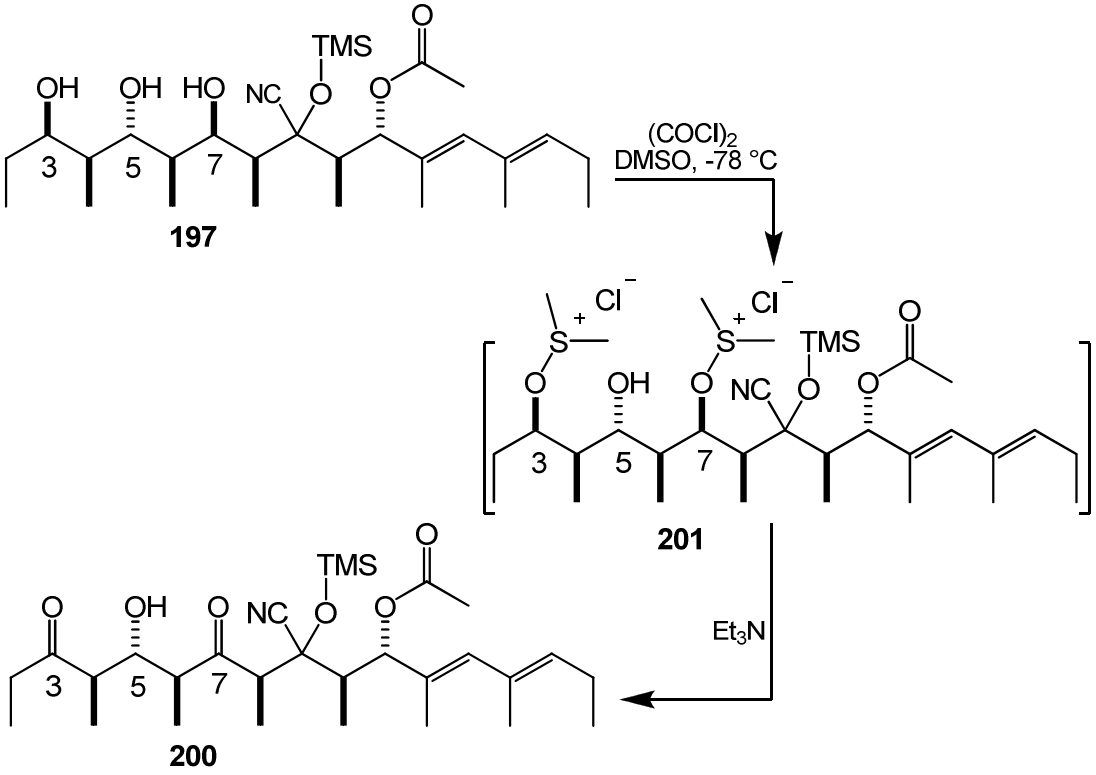
Scheme 2.24 Chemoselective oxidation/protection of triol **197**



a) Et_3SiOTf, 2,6-lutidine; b) $(COCl)_2$, DMSO, Et_3N.

Swern oxidation of triol **197** resulted in a diastereomeric mixture of hydroxy diketone **200** (1.2:1 dr) in excellent yield considering the situations (**Scheme 2.24**). Taking into account the selective formation of **199** and the mechanism of Swern oxidation,[72] this result is rationalized by the formation of intermediate **201** as the kinetically favored species which upon addition of the base gives the desired hydroxy diketone **200** (**Scheme 2.25**).

Scheme 2.25 Proposed mechanism for the chemoselective oxidation of **197**

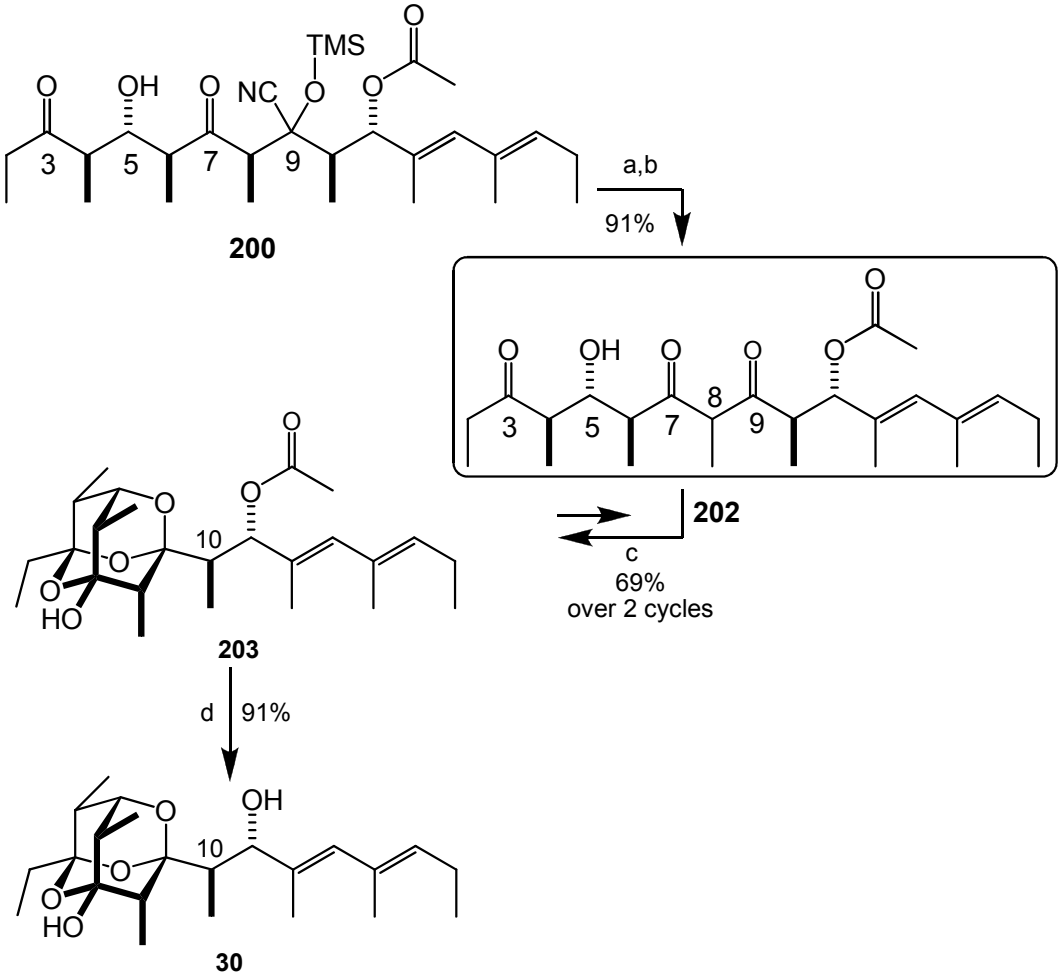


According to the synthetic plan (**Scheme 2.12**), removal of both *O*-trimethylsilyl-cyanohydrin and acetate ester protecting groups from the diastereomeric mixture of **200** should form the desired linear precursor **114a** that can be used in further cyclization studies. Unfortunately, all efforts to remove acetate ester at C11-OH led to decomposition of the starting material. Since the removal of the acetate group was not successful, removal of the *O*-trimethylsilyl-cyanohydrin moiety should lead to *O*-acetate-C11-**114b** (R = Ac) that has all the necessary functionalities to form the desired trioxaadamantane ring system. Subsequent removal of the acetate moiety after formation of the trioxaadamantane should give the desired natural product muamvatin (**30**).

Hydrolysis of the trimethylsilyl group with HF·pyridine gave a diastereomeric mixture of compounds that was not characterized, but was immediately subjected to a

slurry of chromatography silica gel in ethyl acetate to remove the cyanohydrin moiety (**Scheme 2.26**). Interestingly, a mixture of two C8-epimeric forms of the 114b (R = Ac) was produced (ca. 65% of the mixture; identified by two quartets at ca. δ_H 4.02 and 4.00 ppm and signals at δ_C 59.9 and 61.8) with small amounts of enol (ca. 14% of the mixture; identified by the signal at ca. δ_H 16.97 ppm) and hemiacetal (ca. 10% of the mixture; identified by the signal at ca. δ_H 4.99 ppm and acetal carbon at δ_C at 105.0 ppm) (**Figure 2.8**). The diastereomeric mixture **202** was remarkably stable to silica gel chromatography and remained intact while stored in $CDCl_3$ at room temperature for several days.

Scheme 2.26 Preparation of the precursor **202**



a) HF·Py/Py, H_2O (cat.); b) SiO_2, EtOAc; c) HF·Py/Py, H_2O (cat.); d) DIBAL-H, THF, -78 ºC.

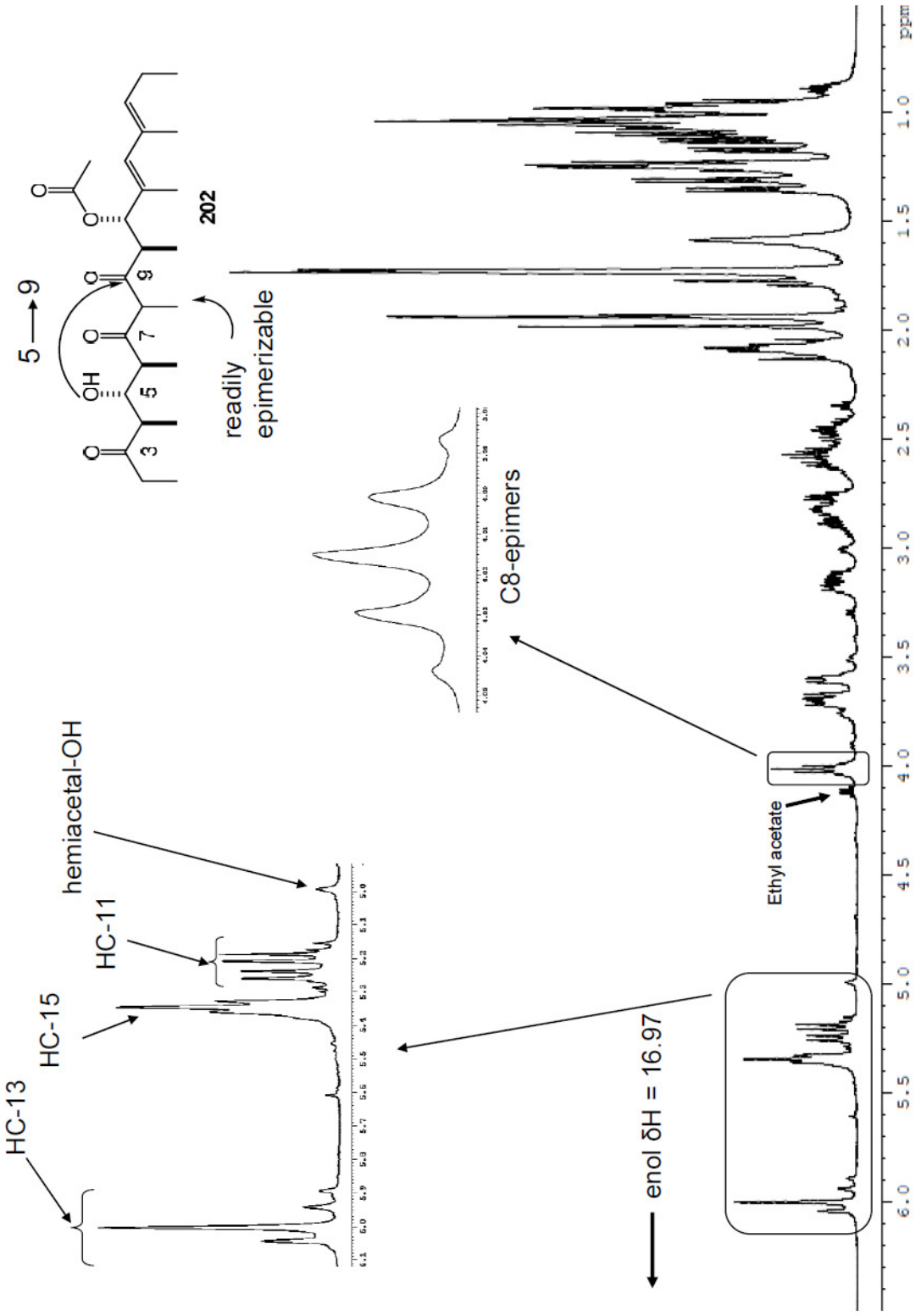


Figure 2.8 ^{1}H NMR spectrum of **202**

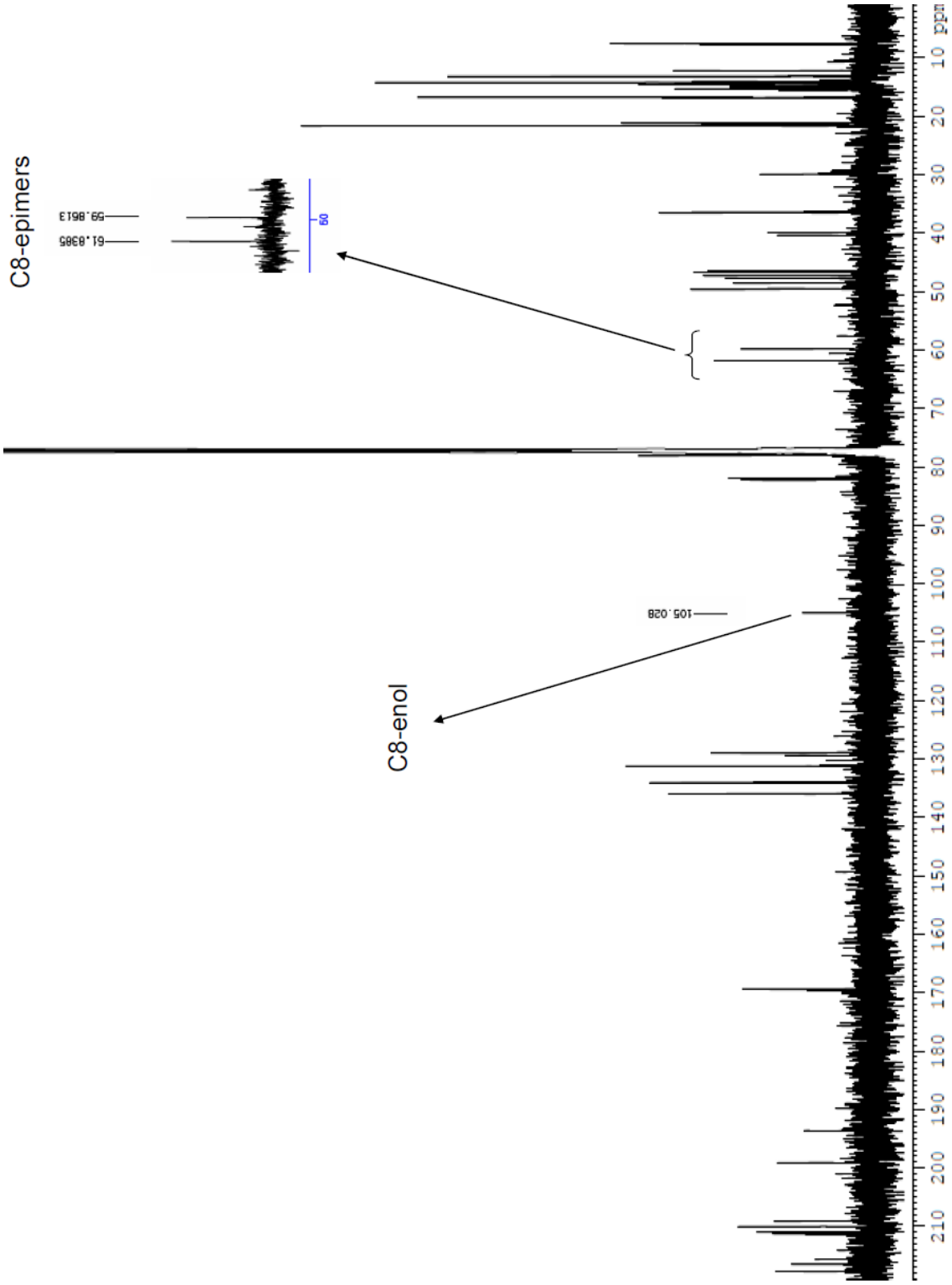


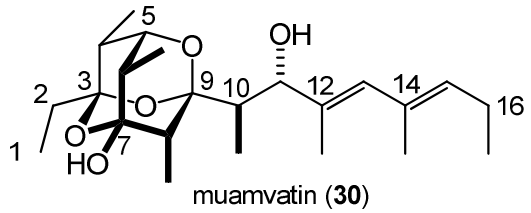
Figure 2.9 ^{13}C NMR spectrum of **202**

Looking back to the earlier studies in formation of the trioxaadamantane ring system (**Section 1.4**) suggested several different mild conditions. Based on the previous work by Paterson et al.[31], subjecting the diastereomeric mixture **202** to chromatography silica gel (Merck kieselgel 60 F_{254}) for 18 hours did not form the desired trioxaadamantane ring system and resulted in full recovery of the starting material. However, exposing the diastereomeric mixture **202** to imidazole in $CDCl_3$ as suggested by Ward et al.[73] changed the ratio between tautomers (ca. the hemiacetal ratio increased to 40% of the reaction mixture after 5 days), it did not result in formation of the desired trioxaadamantane ring system **203**. Subsequently, treatment of **202** with HF·pyridine as reported by Hoffmann et al.[33] for 10 days at ambient temperature resulted in formation of the desired trioxaadamantane ring system **203** (46%) as the predominant component in the reaction mixture (ca, 50% conversion by ^{1}H NMR of the crude reaction mixture). Re-treatment of the recovered starting material under the same reaction conditions provided an additional amount of **203** (69% after two cycles) along with recovered **202** (21%) (**Scheme 2.26**). Finally, removal of the acetate protecting group with DIBAL-H, cleanly produced muamvatin (**30**) ($[\alpha]_D$ +60; *c* 0.13, CH_2Cl_2), that gave spectroscopic data (MS, IR, ^{1}H and ^{13}C NMR) (**Tables 2.1 and 2.2**) that matched perfectly with those reported[30] for isolated ($[\alpha]_D$ +61.1; *c* 0.175 CH_2Cl_2) and synthetic[31] ($[\alpha]_D$ +62; *c* 0.08 CH_2Cl_2) muamvatin (**30**).

Interestingly, exposure of muamvatin (**30**) to reaction conditions such as HF·pyridine (conditions used to form the trioxaadamantane ring system) for twenty days at ambient temperature or to imidazole for ten days at 40 ºC in $CDCl_3$ did not show equilibration to any other possible tautomers of precursors **114a** (**114a** = (8*R*/*S*)-*ent*-**71**)

(see **Figure 1.13**). Such observations suggest that muamvatin is the most thermodynamically stable tautomer from **114a** consistent with the calculations.[29] Thus, the formation of the trioxaadamantane ring system is likely to be governed by an enzyme-mediated process rather than an artifact of isolation.

Table 2.1 ^{13}C NMR ($CDCl_3$) comparison of natural and synthetic muamvatin

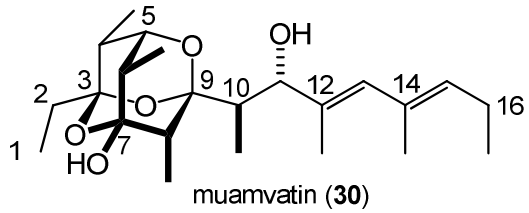


muamvatin (**30**)

Natural[a] δ_C (ppm)[b]	Assignment	Synthetic δ_C (ppm)
5.8	C-1	6.1
29.9	C-2	30.1
102.1	C-3	103.2
37.7	C-4	37.8
78.7	C-5	78.8
43.0	C-6	43.1
97.5	C-7	97.7
35.0	C-8	35.2
105.2	C-9	105.4
40.7	C-10	40.9
79.4	C-11	79.6
134.6	C-12	134.7
132.7	C-13	132.9
131.6	C-14	131.7
132.1	C-15	132.3
21.4	C-16	21.6
14.1	C-17	14.4
16.7	CH_3C-14	16.9
12.3	CH_3C-12	12.5
10.4	CH_3C10	10.6
6.6	CH_3C-8	6.9

[a]Data from Ireland et al.(ref. 45), [b]Chemical shifts for synthetic material are consistently 0.2-0.3 ppm higher than those reported for the natural product presumably due to a different reference standard; we used δc $CDCl_3$ = 77.23.

Table 2.2 ^{1}H NMR ($CDCl_3$) comparison of natural and synthetic muamvatin



muamvatin (**30**)

Natural[a]				Synthetic		
δ_H (ppm)	Multiplicity	*J* (Hz)	Assignment	δ_H (ppm)	Multiplicity	*J* (Hz)
0.96	t	7.46	H_3C-1	0.95	t	7.5
1.69-1.56	dq	14.34, 7.46	HC-2	1.59-1.51	m	
1.18	d	7.93	H_3CC-4	1.18	d	7
1.69	dq	14.34, 7.46	HC-4, HC-2	1.70-1.65	m	
1.69	q	6.93				
3.88	br s		HC-5	3.88	br s	
1.15	d	7.03	H_3CC-6	1.14	d	7
1.97	q	7.03	HC-6, HC-10	2.00-1.92	m	
1.97	dq	9.02, 7.18				
			HOC-7	2.59	br s	
2.10	dq	7.19, 7.52	HC-8, H_2C-16	2.13-2.05	m	
2.10	q	6.74				
1.03	d	6.74	H_3CC-8	1.03	d	7
0.73	d	7.18	H_3CC-10	0.72	t	7
4.40	d	9.02	HC-11	4.40	d	9
			HOC-11	4.38	br s	
1.76	s		H_3CC-12	1.76	br s	
5.87	br s		HC-13	5.87	s	
1.72	s		H_3CC-14	1.72	br s	
5.32	br t	7.19	HC-15	5.31	br dd	7,7
0.98	t	7.52	H_3C-17	0.98	t	7.5

[a]Data and assignment according to ref. 45

2.4 Summary and conclusion

In summary, muamvatin was synthesized in 14 linear steps starting from readily available (-)-**164** in 5.3% overall yield (**Figure 2.9**). This is the first successful synthesis of muamvatin via cyclization of the fully assembled carbon skeleton of the linear precursor to the desired trioxaadamantane ring system. In this approach, two substrate-controlled stereoselective aldol couplings of ketone (-)-**164** and two achiral aldehydes **86** and **73** produced three of the six stereogenic centers existing in muamvatin backbone **114b** (C3, 10, 11; >20:1 dr). The crucial stereogenic center at C5 resulted from an unusual diastereoselective reduction of **175** using super hydride (7:1 dr). The C6 stereogenic center existed in the starting ketone (-)-**164**, that was prepared form ketone (-)-**9a** in three steps and 67% yield. Moreover, this synthesis is the first example of the use of allyl ethers as viable protecting groups with mild removal using a ruthenium based catalyst **190** in the presence of other sensitive functionalities. The chemoselective double Swern oxidation reaction to overcome the oxidation state manipulation problem on the fully assembled carbon skeleton of muamvatin precursor is noteworthy.

Despite the failure encountered in the attempted formation of acyclic precursor **114a** and studying its cyclization modes, precursor **202** was successfully cyclized to the desired trioxaadamantane **203**. Regarding the conditions used to form the desired trioxaadamantane ring system (exposure to HF·pyridine for 10 days) suggested that the formation of such trioxaadamantane ring system is not a facile process that could readily happen under the conditions used for isolation, such as exposure to silica gel or different solvent systems; but, it might be the result of an enzymatic process.

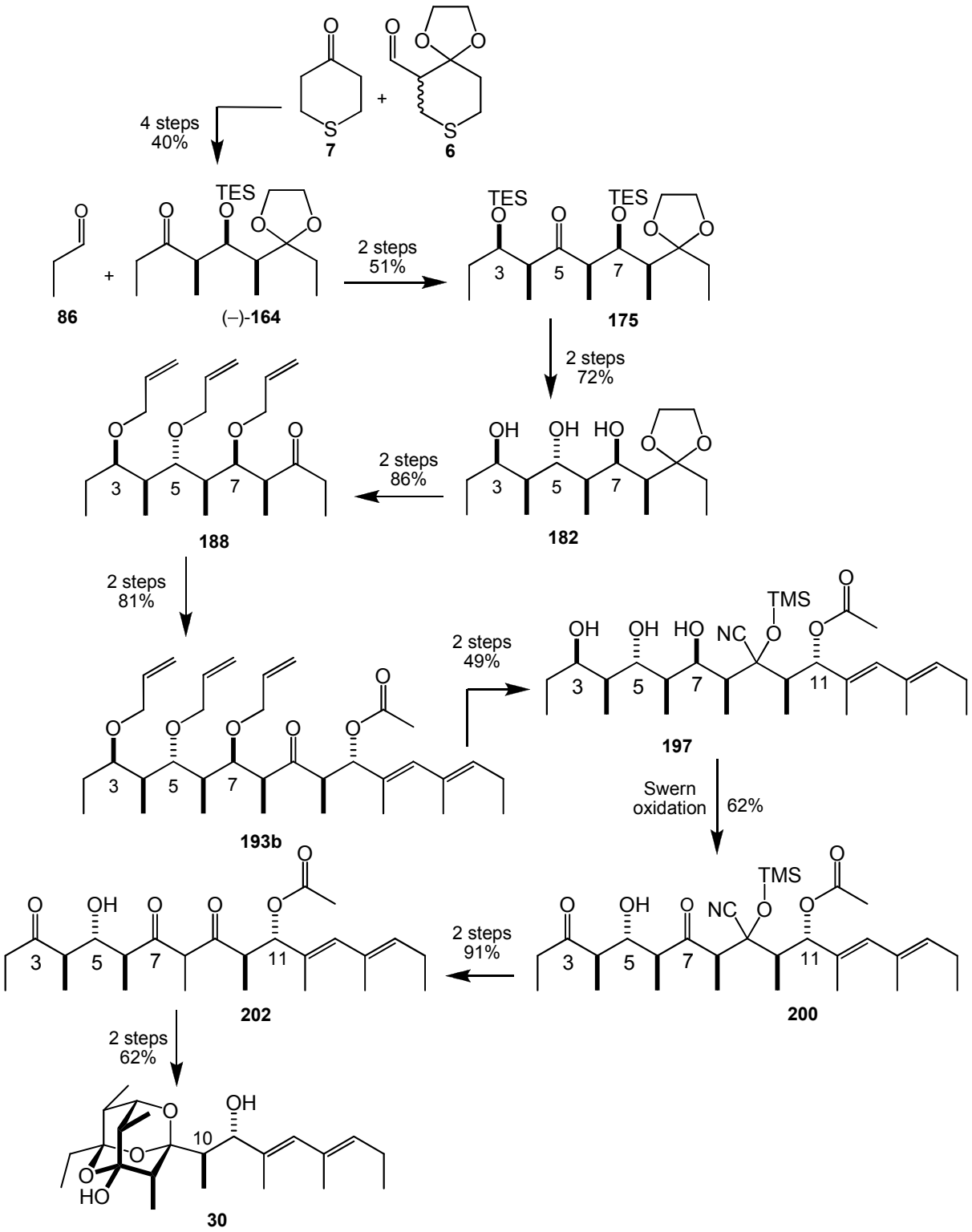


Figure 2.10 Summary of the synthetic route

3. EXPERIMENTAL

3.1 General methods

Anhydrous solvents were distilled under argon atmosphere as follows: Terahydrofuran (THF) and diethyl ether from benzophenone sodium ketyl; CH_2Cl_2 from CaH_2; MeOH from $Mg(OMe)_2$; dimethyl sulfoxide (DMSO) from CaH_2. All experiments involving air and/or moisture sensitive compounds were conducted either in an oven dried round-bottle flask capped with a rubber septum, and attached via a needle and connecting tubing to an argon manifold equipped with mercury bubbler (ca. 5 mm positive pressure of argon) or in a Schlenk flask capped with a rubber stopper, and attached via connecting tubing to an argon manifold equipped with mercury bubbler (ca. 5 mm positive pressure of argon). Low temperature baths were: ice/water (0 ºC), CO_2/CH_3CN (-50 ºC), and CO_2(s)/acetone (-78 ºC). Unless otherwise noted, reaction temperatures refer to that of the bath.

Preparative TLC (PTLC) was carried out on glass plates (20×20 cm) pre-coated (0.25 mm) with silica gel 60 F_{254}. Materials were detected by visualization under an ultraviolet lamp (254 nm) and/or by treating a 1 cm vertical strip removed from the plate with a solution of phosphomolybdic acid (5%) containing a trace of ceric sulfate in aq sulfuric acid (5% *v/v*), followed by charring on a hot plate. TLC was carried out on glass plates (1×3 cm) pre-coated (0.25 mm) with silica gel 60 F_{254} and was visualized in the same manner as that described for PTLC.

Concentration refers to removal of volatiles with a rotary evaporator under vacuum supplied by a water aspirator. Evacuation at ca. 0.5 torr with a vacuum pump generally followed rotary evaporation.

Flash column chromatography (FCC) was performed according to Still et al.[74] with Merck silica gel 60 (40-63 μm). All mixed solvent eluents are reported as *v/v* solutions. Unless otherwise noted, all reported compounds were homogeneous by thin layer chromatography (TLC) and by ^{1}H NMR spectroscopy.

Spectral data

High resolution mass spectra (HRMS) and low resolution mass spectra (LRMS) were obtained on a VG 70E double focusing high resolution spectrometer; only partial data are reported. Alternatively, HRMS was obtained on a LC-MS/MS time-of-flight high resolution spectrometer with electrospray ionization (ESI) from acetonitrile solution.

IR spectra were recorded on a Fourier transform interferometer using a diffuse reflectance cell (DRITF) or by casting a thin film from $CDCl_3$ solution onto a KBr disc; only diagnostic and/or intense peaks are reported. Unless otherwise noted all experiments used DRITF.

Unless otherwise noted, NMR spectra were measured in $CDCl_3$ solution at 500 MHz for ^{1}H and 125 MHz for ^{13}C. Signals due to the solvent (^{13}C NMR spectroscopy) or residual protonated solvent (^{1}H NMR spectroscopy) served as the internal standard: $CDCl_3$ (7.26 δ_H, 77.23 δ_C); C_6D_6 (7.16 δ_H, 128.39 δ_C). The ^{1}H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), ap (apparent); the list of coupling constants (*J*) corresponds to the order of the multiplicity assignment. Coupling constants (*J*) are reported to the nearest 0.5 Hz (digital resolution ca. 0.2 Hz/pt) or the nearest 0.1 Hz (digital resolution ca. 0.03 Hz/pt). The ^{1}H NMR assignments were made based on chemical shift and multiplicity

and were confirmed, where necessary, by homonuclear decoupling and/or two-dimensional correlation experiments (gCOSY, gHSQC, gHMBC). The ^{13}C NMR assignments were made on the basis of chemical shift and multiplicity (as determined by ^{13}C-DEPT or gHSQC) and were confirmed, where necessary, by two-dimensional $^{1}H/^{13}C$ correlation experiments (gHSQC and/or gHMBC). The multiplicity of ^{13}C NMR signals refers to the number of attached H's (i.e., s = C, d = CH, t = CH_2, q = CH_3).

Specific rotation ($[\alpha]_D$) are the average of 5 determinations at ambient temperature using a 1 mL, 10 cm cell; the units are 10^{-1} deg cm^2 g^{-1}, the concentration (*c*) are reported in g/100 mL, and the values are rounded to reflect the accuracy of the measured concentrations (the major source of error).

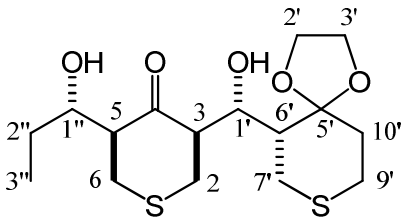
Materials

The following compounds and reagents were prepared as described previously: **7**;[2] **6**,(±)-**9a**,[3] and (+)-*O*-TES-**9a** (.98% ee);[5] **73**;[32] **190**;[64] **140**;[13] W-2 Raney nickel;[75] IBX;[76] $TiCl_3(O^iPr)$;[77] KCN·18-crown-6;[70] 2,6-lutidine was distilled from CaH_2 under argon and stored over 4Å molecular sieves; Et_3N and $^iPr_2NEt$ were distilled from CaH_2 under argon atmosphere and stored over KOH; All other reagents were commercially available and unless otherwise noted, were used as received.

Experimental procedures and characterization data

Spectral data and experimental procedures are presented in order, by compound number with the exception of muamvatin (**30**) that appears at the end.

(3*R*,5*S*)-*rel*-3-((*S*)-Hydroxy((*R*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)methyl)-5-((*S*)-1-hydroxypropyl)tetrahydro-4*H*-thiopyran-4-one (120)



120

This procedure was adapted from Ward et al.[4] A solution of $TiCl_3(O^iPr)$ (0.5 M in CH_2Cl_2; 35 mL, 18 mmol) was added over 10 minutes to a stirred solution of (±)-**9a** (4.90 g, 16 mmol) in CH_2Cl_2 (100 mL) at –78 °C. After 10 min, $^iPr_2EtN$ (2.8 mL, 2.1 g, 16 mmol) was added slowly to the reaction mixture. After 1 h, propanal (1.2 mL, 0.97 g, 17 mmol) was added, and after 1 h, $^iPr_2EtN$ (4.2 mL, 3.1 g, 24 mmol) was added. After 2 h, the reaction was quenched by addition of saturated aq NH_4Cl (50 mL) with vigorous stirring. The cooling bath was removed and the reaction mixture was allowed to warm to ambient temperature over 20 min. Celite® (30 g) followed by Et_2O (150 mL) were added to the mixture (this process cleared the emulsion). After 5 min, the organic (top) layer was decanted and filtered through a sintered glass funnel containing a pad of Na_2SO_4 (20 g, 2 cm) on top of a pad of Celite® (20 g, 2 cm). The remaining lower layer in the reaction vessel was extracted twice with Et_2O and twice with ethyl acetate by addition of the solvent with stirring followed after 5 min by decanting and filtering as above. The combined filtrates were concentrated to give a crude product whose ^1H NMR spectrum suggested the presence of a 1.5:1 mixture of **120** (>20:1 dr) and (±)-**9a**, respectively. Fractionation of the crude by FCC (40% ethyl acetate in hexane) gave recovered (±)-**9a** (1.5 g, 30%) and the titled compound (3.1 g, 53%).

IR (DRITF) ν_{max}: 3521, 1693 cm^{-1}.

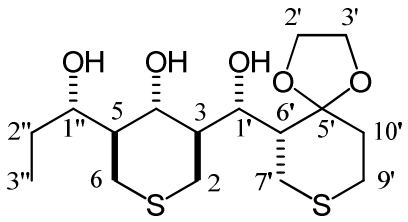
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.27 (1H, ddd, *J* = 6, 6, 7 Hz, HC-1'), 3.99-3.87 (4H, m, H_2C-2', H_2C-3'), 3.71-3.65 (1H, m, HC-1''), 3.24 (1H, ddd, *J* = 4.5,4.5, 11.5 Hz, HC-3), 3.10 (1H, dd, *J* = 11.5, 14 Hz, HC-2), 2.98-2.86 (8H, m, HC-2, HC-5, H_2C-6, H_2C-7', HO ×2), 2.74 (1H, ddd, *J* = 3, 8, 12.5 Hz, HC-9'), 2.63 (1H, ddd, *J* = 3, 8, 12.5 Hz, HC-9'), 2.11 (1H, ddd, *J* = 5, 5.5, 6 Hz, HC-6'), 1.88 (1H, ddd, *J* = 3, 8, 13 Hz, HC-10'), 1.72 (1H, ddd, *J* = 3, 8, 13 Hz, HC-10'), 1.58 (1H, ddq, *J* = 4, 14, 7.5 Hz, HC-2''), 1.50 (1H, ddq, *J* = 7, 14, 7.5 Hz, HC-2''), 0.98 (3H, t, *J* = 7.5 Hz, H_3C-3'').

^{13}C NMR (125 MHz, $CDCl_3$): δ 217.0 (s, C-4), 109.1 (s, C-5'), 72.8 (d, C-1''), 70.1 (d, C-1'), 64.9 (t, C-2'), 64.3 (t, C-3'), 59.6 (d, C-5), 57.2 (d, C-3), 47.4 (d, C-6'), 36.2 (t, C-2), 35.5 (t, C-6), 35.1 (t, C-10'), 28.6 (t, C-7'), 27.0 (t, C-2''), 26.8 (t, C-9'), 10.0 (q, C-3'').

LRMS (EI), *m/z* (relative intensity): 362 ($[M]^+$, 4), 276 (16), 159 (24), 195 (29), 132 (71), 116 (10), 99 (100), 86 (18), 54 (30).

HRMS (EI), *m/z* calcd for $C_{16}H_{26}O_5S_2$: 362.1222; found: 362.1211.

(3*S*,4*S*,5*S*)-*rel*-3-((*S*)-Hydroxy((*R*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)methyl)-5-((*S*)-1-hydroxypropyl)tetrahydro-2*H*-thiopyran-4-ol (121)



121

$NaBH_4$ (611 mg, 16.2 mmol) was added to a stirred solution of **120** (2.93 g, 8.08 mmol, 0.08M) in THF (85 mL) and methanol (15 mL) at –78 °C. After 1 h, aq NaOH (0.4 M; 50 mL) was added and the mixture was allowed to warm to ambient temperature. After 1.5 h, the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, and concentrated to give a crude product (3 g) whose ^{1}H NMR spectrum indicated the presence of a 12:1 mixture of alcohols. Fractionation of the crude by FCC (20% ether in CH_2Cl_2) gave the titled compound (2.58 g, 88%).

IR (DRIFT) ν_{max}: 3467, 3342 cm^{-1}.

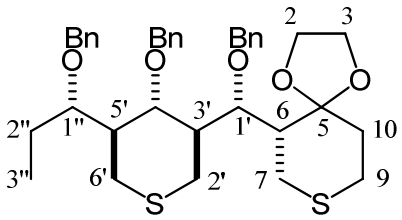
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.23 (1H, d, *J* = 9 Hz, HC-1'), 4.15-3.96 (4H, m, H_2C-2', H_2C-3'), 3.68 (1H, ddd, *J* = 3, 7, 7.5 Hz, HC-1''), 3.67 (1H, dd, *J* = 9, 9.5 Hz, HC-4), 3.04 (1H, dd, *J* = 12, 14 Hz, HC-7'), 2.82 (1H, ddd, *J* = 2.5, 12.5, 13.5 Hz, HC-9'), 2.68 (1H, ddd, *J* = 2.5, 3.5, 14 Hz, HC-7'), 2.58 (1H, ddd, *J* = 2.5, 3.5, 13.5 Hz, HC-6), 2.52 (1H, dddd, *J* = 2.5, 3.5, 4, 13.5 Hz, HC-9'), 2.42 (1H, ddd, *J* = 2.5, 3.5, 14 Hz, HC-2), 2.30 (1H, dd, *J* = 12, 13.5 Hz, HC-6), 2.30 (1H, dd, *J* = 11.5, 14 Hz, HC-2), 2.17 (1H, ddd, *J* = 2.5, 4, 14 Hz, HC-10'), 2.08 (1H, br dd, *J* = 3.5, 12 Hz, HC-6'), 1.96 (1H, dddd, *J* = 3.5, 9, 9, 11.5 Hz, HC-3), 1.89 (1H, dddd, *J* = 3.5, 7, 9.5, 12 Hz, HC-5), 1.72 (1H, ddd, *J* = 3.5, 12.5, 14 Hz, HC-10'), 1.61 (1H, ddq, *J* = 3, 14, 7.5 Hz, HC-2''), 1.43 (1H, ddq, *J* = 7.5, 14, 7.5 Hz, HC-2''), 0.98 (3H, t, *J* = 7.5 Hz, H_3C-3'').

^{13}C NMR (125 MHz, $CDCl_3$) δ 110.7 (s, C-5'), 79.3 (d, C-4), 76.3 (d, C-1'), 74.7 (d, C-1''), 64.9 (t, C-2'), 64.3 (t, C-3'), 50.1 (d, C-5), 46.7 (d ×2, C-3, C-6'), 36.3 (t, C-10'), 29.5 (t, C-2), 29.0 (t, C-6), 27.0 (t, C-2''), 26.7 (t, C-9'), 25.7 (t, C-7'), 9.5 (q, C-3'').

LRMS (EI), *m/z* (relative intensity): 364 ([M]$^+$, 25), 346 (22), 302 (27), 195 (29), 284 (20), 159 (40), 132 (100), 117 (31).

HRMS (EI), *m/z* calcd for $C_{16}H_{28}O_5S_2$: 364.1378; found: 364.1376.

(*R*)-*rel*-6-((*S*)-(Benzyloxy)((3*S*,4*S*,5*S*)-4-(benzyloxy)-5-((*S*)-1-(benzyloxy)propyl)tetrahydro-2*H*-thiopyran-3-yl)methyl)-1,4-dioxa-8-thiaspiro[4.5]decane (128).



128

A solution of triol **121** (420 mg, 1.15 mmol) in THF (7 mL) was added slowly via syringe to a suspension of KH (oil removed by washing with hexane; 150 mg, 3.7 mmol) in THF (7 ml) at 0 °C. After 5 min, BnBr (0.68 mL, 5.7 mmol) was added slowly to the reaction mixture. The mixture was stirred at 0 °C for 10 min and then allowed to warm to ambient temperature. After 1 h (reaction complete by TLC analysis), the reaction mixture was cooled to 0 °C and quenched by slow addition of MeOH (1 mL) (Caution: H_2 evolution). The mixture diluted with CH_2Cl_2 and washed sequentially with water and brine. The aqueous layers were back extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (10% ethy lacetate in hexane) to give the titled compound (720 mg, 98%).

IR (neat) ν_{max}: 3029 cm^{-1}.

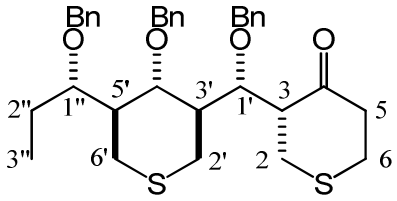
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.24 (15H, m, Ph), 4.74 and 4.32 (2H, d ×2, *J* = 11.5 Hz, H_2CPh), 4.62 and 4.38 (2H, d ×2, *J* = 11.5 Hz, H_2CPh), 4.59 and 4.56 (2H, d ×2, *J* = 11.5 Hz, H_2CPh), 3.98 (1H, br dd, *J* = 2, 3 Hz, HC-1'), 3.88-3.79 (3H, m, H_2C-2, HC-3), 3.67 (1H, ddd, *J* = 2, 3, 10.5 Hz, HC-1''), 3.52-3.48 (1H, m, HC-3), 3.36 (1H, dd, *J* = 9.5, 9.5 Hz, HC-4), 3.03 (1H, dd, *J* = 11, 14 Hz, HC-7), 2.88-2.82 (2H, m, HC-2', HC-9), 2.78 (1H, ddd, *J* = 2, 2.5,13 Hz, HC-6'), 2.72 (1H, ddd, *J* = 2, 3, 14 Hz, HC-7), 2.58 (1H, dd, *J* = 11.5, 13 Hz, HC-6'), 2.54-2.46 (3H, m, HC-3', HC-5', HC-9), 2.42 (1H, dd, *J* = 11.5, 13 Hz, HC-2'), 2.37 (1H, ddd, *J* = 3, 4.5, 11 Hz, HC-6), 2.10 (1H, ddd, *J* = 3, 4, 13.5 Hz, HC-10), 1.71 (1H, ddd, *J* = 3.5, 12.5, 13,5 Hz, HC-10), 1.63-1.52 (1H, m, HC-2''), 1.51-1.41 (1H, m, HC-2''), 0.95 (3H, t, *J* = 7.5 Hz, H_3C-3'').

^{13}C NMR (125 MHz, $CDCl_3$) δ 139.10 (s, Ph), 139.06 (s, Ph), 138.9 (s, Ph), 128.53 (d ×2, Ph), 128.52 (d ×2, Ph), 128.49 (d ×2, Ph), 128.2 (d ×2, Ph), 127.8 (d ×2, Ph), 127.73 (d, Ph), 127.70 (d, Ph), 127.4 (d, Ph), 127.0 (d ×2, Ph), 109.4 (s, C-5), 80.2 (d, C-1''), 78.0 (d, C-4), 77.4 (d, C-1'; confirmed by DEPT), 73.4 (t, CH_2Ph), 71.8 (t, CH_2Ph), 70.7 (t, CH_2Ph), 64.6 (t, C-2), 64.5 (t, C-3), 50.4 (d, C-3'), 49.1 (d, C-6), 48.0 (d, C-5'), 36.6 (t, C-10), 30.2 (br) (t, C-6'), 29.2 (t, C-7), 27.3 (t, C-2'), 26.9 (t, C-9), 23.1 (t, C-2''), 11.3 (q, C-3'').

LRMS (EI), *m/z* (relative intensity): 634 ($[M]^+$, 1), 543 (3), 435 (5), 279 (11), 132 (11), 99 (25), 91 (100).

HRMS (EI), *m/z* calcd for $C_{37}H_{46}O_5S_2$: 634.2786; found: 634.2778.

(*R*)-*rel*-3-((*S*)-(Benzyloxy)((3*S*,4*S*,5*S*)-4-(benzyloxy)-5-((*S*)-1-(benzyloxy)propyl)tetrahydro-2*H*-thiopyran-3-yl)methyl)dihydro-2*H*-thiopyran-4(3*H*)-one (129).



129

A suspension of Amberlyst®-15 (2.24 g) and **128** (560 mg, 0.883 mmol) in acetone (40 mL) was heated under reflux. After 2 h (reaction complete by TLC analysis), the cooled mixture was decanted and the Amberlyst®-15 washed with CH_2Cl_2. The combined organic layers were washed with saturated aq $NaHCO_3$, dried over Na_2SO_4, concentrated, and fractionated by FCC (20% ethyl acetate in hexane) to give the titled compound (520 mg, 95%).

IR (DRIFT) ν_{max}: 3030, 1696 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.27 (15H, m, Ph), 4.66 and 4.56 (2H, d ×2, *J* = 11 Hz, H_2CPh), 4.62 and 4.38 (2H, d ×2, *J* = 11.5 Hz, H_2CPh), 4.54 and 4.30 (2H, d ×2, *J* = 10.5 Hz, H_2CPh), 4.24 (1H, br d, *J* = 7 Hz, HC-1'), 3.67 (1H, br d, *J* = 10 Hz, HC-1''), 3.35 (1H, dd, *J* = 9.5, 10 Hz, HC-4'), 3.26 (1H, ddd, *J* = 4, 7, 10.5 Hz, HC-3), 3.13 (1H, br dd, *J* = 3.5,13.5 Hz, HC-2), 2.93-2.79 (5H, m, HC-2, HC-2', H_2C-6, HC-6'), 2.74 (1H, ap ddd, *J* = 4.5, 5, 13 Hz, HC-5), 2.65-2.57 (2H, m, HC-2', HC-5), 2.49-2.38 (2H, m, HC-

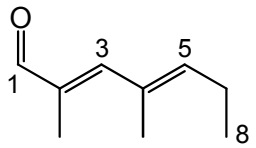
5', HC-6'), 2.30 (1H, br dd, J = 10, 11.5 Hz, HC-3'), 1.55-1.40 (2H, m, H_2C-2''), 0.96 (3H, t, J = 7 Hz, H_3C-3'').

^{13}C NMR (125 MHz, $CDCl_3$) δ 210.3 (s, C-4), 138.8 (s, Ph), 138.2 (s, Ph), 138.0 (s, Ph), 128.68 (d ×2, Ph), 128.65 (d ×2, Ph), 128.5 (d ×2, Ph), 128.1 (d, Ph), 128.0 (d ×4, Ph), 127.9 (d, Ph), 127.8 (d ×2, Ph), 127.7 (d, Ph), 80.0 (d, C-1''), 78.5 (d, C-4'), 78.4 (d, C-1'), 74.5 (t, CH_2Ph), 71.6 (t, CH_2Ph), 70.8 (t, CH_2Ph), 56.9 (d, C-3), 48.9 (d, C-3'), 47.7 (d, C-5'), 44.7 (t, C-5), 33.7 (t, C-2), 31.4 (t, C-6), 31.0 (t, C-2'), 27.5 (t, C-6'), 23.0 (t, C-2''), 11.4 (q, C-3'').

LRMS (CI, NH_3), *m/z* (relative intensity): 608 ($[M+18]^+$, 2), 483 (33), 375 (20), 285 (6), 269 (5), 108 (18), 105 (17), 91 (100), 77 (5).

HRMS (ESI), *m/z* calcd for $C_{35}H_{42}O_4S_2$+Na: 613.2416; found: 613.2404.

(2E,4E)-2,4-dimethylhepta-2,4-dienal (73).

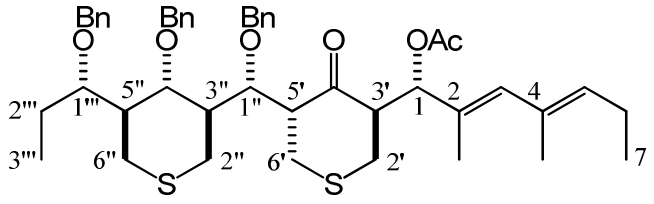


73

IBX (1.22 g, 4.36 mmol) was added to a stirred solution of **130** (510 mg, 3.63 mmol) in DMSO (5 mL) in ambient temperature. The reaction was done by TLC after 3h. The reaction mixture was diluted by ethyl acetate (150 mL) and extracted twice by $NaHCO_3$ solution. The organic layer were dried over Na_2SO_4, concentrated, and fractionated by FCC (15% ethyl acetate in hexane) to give the titled compound in (381 mg, 88%).

The spectral data were matched perfectly with what is reported by Hoffmann et al.[32]

(*S*,2*E*,4*E*)-*rel*-1-((3*R*,5*R*)-5-((*S*)-Benzyloxy((3*S*,4*S*,5*S*)-4-(benzyloxy)-5-((*S*)-1-(benzyloxy)propyl)tetrahydro-2*H*-thiopyran-3-yl)methyl)-4-oxotetrahydro-2*H*-thiopyran-3-yl)-2,4-dimethylhepta-2,4-dienyl Acetate (131b).



131b

A solution of **129** (190 mg, 0.32 mmol) in CH_2Cl_2 (2.5 ml) was added dropwise via syringe to a stirred solution of (*c*-Hex)$_2$BCl (1 M in hexane; 0.70 ml, 0.70 mmol), and Et_3N (0.140 mL, 0.96 mmol) in CH_2Cl_2 (2 mL) at 0 °C. After 30 min, the reaction mixture was cooled to –78 °C and a solution of the **73** (88 mg, 0.64 mmol) in CH_2Cl_2 (1 mL) was added to the reaction mixture. After 2 h, MeOH (3 mL), phosphate buffer (pH 7; 6 mL), and 30% aq H_2O_2 (1.2 mL) were sequentially added with vigorous stirring. The reaction mixture was transferred to a 0 °C bath and after 15 min, the excess H_2O_2 was quenched by slow addition of saturated aq Na_2SO_3 (2 mL). The mixture was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4, and concentrated to give the crude product (310 mg) whose ^{1}H NMR spectrum indicted the presence of a single adduct (>20:1 dr) along with **129** (ca. 75% conversion). The crude was fractionated by FCC (10% ethyl acetate in hexane) to give an inseparable mixture of aldol-adduct-**131a** and **129** (214 mg). Acetic anhydride (0.66 mL, 6.4 mmol), ^{i}Pr$_2$EtN (1.2 mL, 6.9 mmol), and DMAP (8 mg, 0.06 mmol) were added sequentially to a stirred

solution of the above mixture in CH_2Cl_2 (5 mL) at 0 °C. After 2 h, the mixture was diluted with CH_2Cl_2 (20 mL) and washed with saturated aq $NaHCO_3$, dried over Na_2SO_4, concentrated, and fractionated by FCC (10% ethyl acetate in hexane) to give recovered **129** (40 mg, 21%) and the titled compound (170 mg, 69%).

IR (DRIFT) ν_{max}: 3031, 1741, 1706 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.22 (15H, m, Ph ×3), 6.08 (1H, s, HC-3), 5.88 (1H, d, *J* = 11 Hz, HC-1), 5.36 (1H, ap t, *J* = 7 Hz, HC-5), 4.64 and 4.418 (2H, d ×2, *J* = 11.5 Hz, H_2CPh), 4.61 and 4.51 (2H, d ×2, *J* = 11.5 Hz, H_2CPh), 4.420 and 4.30 (2H, d ×2, *J* = 10.5 Hz, H_2CPh), 4.31 (1H, br d, *J* = 5 Hz, HC-1''), 3.64 (1H, br d, *J* = 10.5 Hz, HC-1'''), 3.43 (1H, ddd, *J* = 5, 6, 10.5 Hz, HC-5'), 3.32 (1H, ap dd, *J* = 9.5, 10 Hz, HC-4''), 3.04-2.92 (3H, m, HC-2', HC-3', HC-6'), 2.87-2.78 (3H, m, HC-2'', HC-6', HC-6''), 2.61-2.54 (2H, m, HC-2', HC-2''), 2.49-2.40 (2H, m, HC-5'', HC-6''), 2.16 (1H, br dd, *J* = 10.5, 11 Hz, HC-3''), 2.13-2.05 (2H, m, H_2C-6), 1.82 (3H, s, H_3CCO), 1.73 (3H, s, H_3CC-2), 1.68 (3H, s, H_3CC-4), 1.62 (1H, br dq, *J* = 14, 7 Hz, HC-2'''), 1.42 (1H, ddq, *J* = 10.5, 14, 7 Hz, HC-2'''), 0.98 (3H, t, *J* = 7.5 Hz, H_3C-7), 0.92 (3H, t, *J* = 7 Hz, H_3C-3''').

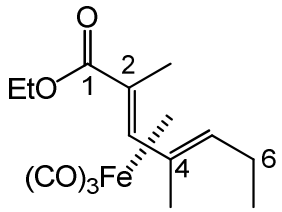
^{13}C NMR (125 MHz, $CDCl_3$) δ 209.9 (s, C-4'), 169.7 (s, COO), 138.8 (s, Ph), 138.4 (s, Ph), 138.2 (s, Ph), 136.4 (d, C-3), 134.5 (d, C-5), 131.2 (s, C-2 or C-4), 128.66 (d ×4, Ph), 128.56 (d ×2, Ph), 128.3 (d, C-2 or C-4), 128.16 (d ×2, Ph), 128.13 (d ×2, Ph), 128.03 (d, Ph), 128.00 (d ×2, Ph), 127.82 (d, Ph), 127.78 (d, Ph), 80.1 (d, C-1'''), 79.4 (d, C-1), 78.6 (d, C-4''), 77.2 (d, C-1''), 74.2 (t, CH_2Ph), 71.6 (t, CH_2Ph), 70.6 (t, CH_2Ph), 53.9 (d, C-3'), 53.4 (d, C-5'), 49.6 (d, C-3''), 47.8 (d, C-5''), 34.0 (t, C-6'), 33.3 (t, C-2'), 31.3 (t, C-2''),

27.8 (t, C-6"), 22.8 (t, C-2'"), 21.6 (t, C-6), 21.3 (t, CH_3CO), 16.8 (t, CH_2C-2), 14.2 (t, C-7), 12.7 (t, CH_3C-4), 11.6 (t, C-3'").

LRMS (EI), *m/z* (relative intensity): 770 ($[M]^+$, 0.04), 710 (0.4), 519 (6), 403 (4), 345 (5), 274 (11), 248 (7), 191 (7), 108 (20), 91 (100).

HRMS (ESI), *m/z* calcd for $C_{46}H_{58}O_6S_2$+Na: 793.3567; found: 793.3570.

Tricarbonyl[(2,3,4,5-η)-ethyl (2*E*,4*E*)-2,4-dimethyl-2,4-heptadienoate]iron (137).



(±)-**137**

A stirred solution of $Fe_2(CO)_9$ (3.00 g, 8.24 mmol) and 76 (1.00 g, 5.48 mmol) in benzene (40 mL) was heated under reflux. After 2 h, additional $Fe_2(CO)_9$ (1.50 g, 4.12 mmol) was added. After 1 h, the mixture was allowed to cool to ambient temperature and was filtered through a pad of Celite®. The combined filtrate and washings were concentrated, and fractionated by FCC (10% ethyl acetate in hexane) to give the titled compound (0.96 g, 54%).

IR (DRIFT) ν_{max}: 2044, 1985, 1970, 1691 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (1H, s, HC-3), 4.18 (1H, dq, *J* = 10.5, 7.5 Hz, HCO), 4.05 (1H, dq, *J* = 10.5, 7.5 Hz, HCO), 2.47 (1H, dd, *J* = 6, 7.5 Hz, HC-5), 2.17 (3H, s, H_3CC-4), 1.99-1.90 (1H, ddq, *J* = 6, 14, 7 Hz, HC-6), 1.70-1.61 (1H, ddq, *J* = 7.5, 14, 7

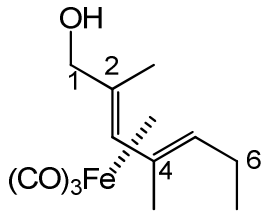
Hz, HC-6), 1.26 (3H, t, *J* = 7 Hz, H_3CCO), 1.12 (3H, t, *J* = 7 Hz, H_3C-7), 1.12 (3H, s, H_3CC-2).

^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1 (s, C-1), 105.7 (s, C-4), 88.1 (d, C-3), 66.8 (d, C-5), 60.7 (t, CH_2O), 52.7 (s, C-2), 24.7 (t, C-6), 19.3 (q, CH_3C-4), 15.6 (q, CH_3C-2), 15.1 (q, C-7), 14.4 (q, CH_3CO).

LRMS (EI), *m/z* (relative intensity): 322 ([M]$^+$, 2), 294 (14), 266 (33), 238 (100), 222 (39), 192 (14), 178 (15), 138 (21), 95 (12).

HRMS (EI), *m/z* calcd for $C_{14}H_{18}FeO_5$: 322.0504; found: 322.0507.

Tricarbonyl[(2,3,4,5-η)-(2*E*,4*E*)-2,4-dimethyl-2,4-heptadien-1-ol]iron (138a).



(±)-**138a**

DIBAL-H (1 M in toluene; 3.1 mL, 3.1 mmol) was added slowly via syringe to a stirred solution of (±)-**137** (503 mg, 1.56 mmol) in THF (20 mL) at –78 °C under argon. After 1 h, the reaction mixture was allowed to warm to ambient temperature over 1 h. The mixture was cooled to 0 °C and the reaction was quenched by sequential addition of ethanol (1 mL) and water (1 mL). The mixture was diluted with ethyl acetate (100 ml), washed with brine (20 ml), dried over Na_2SO_4, concentrated, and fractionated by FCC (15% ethyl acetate in hexane) to give the titled compound (401 mg, 92%).

IR (DRIFT) ν_{max}: 3250, 2035, 1956 cm^{-1}.

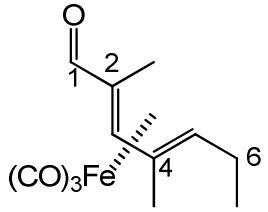
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.08 (1H, s, HC-3), 3.56 (2H, br s, H_2C-1), 2.40 (1H, br s, HO), 2.26 (1H, br t, *J* = 7 Hz, HC-5), 2.13 (3H, s, H_3CC-4), 1.96-1.88 (1H, m, HC-6), 1.68-1.59 (1H, m, HC-6), 1.21 (3H, s, H_3CC-2), 1.08 (3H, t, *J* = 7.5 Hz, H_3C-7).

^{13}C NMR (125 MHz, $CDCl_3$) δ 212.1 (s, CO ×3), 104.1 (s, C-4), 88.8 (d, C-3), 74.2 (t, C-1), 67.9 (s, C-2), 66.7 (d, C-5), 24.7 (t, C-6), 19.2 (q, CH_3C-4), 16.5 (br) (q, CH_3C-2), 15.6 (q, C-7).

LRMS (EI), *m/z* (relative intensity): 280 ($[M]^+$, 3), 252 (37), 224 (53), 178 (100), 175 (39), 162 (50), 123 (39), 107 (38), 81 (44), 67 (38).

HRMS (EI), *m/z* calcd for $C_{12}H_{16}FeO_4$: 280.0398; found: 280.0400.

Tricarbonyl[(2,3,4,5-η)-(2*E*,4*E*)-2,4-dimethyl-2,4-heptadienal]iron (138b).



(±)-**138b**

IBX (260 mg, 0.928 mmol) was added to a stirred solution of (±)-**138a** (200 mg, 0.714 mmol) in THF (7 mL) and DMSO (7 mL) at ambient temperature. After 1.5 h, the reaction mixture was diluted with ethyl acetate, washed sequentially with saturated aq $NaHCO_3$ solution, water and brine, dried over Na_2SO_4, concentrated, and fractionated by FCC (20% ethyl acetate in hexane) to give the titled compound (178 mg, 90%).

IR (DRIFT) ν_{max}: 2045, 2875, 1975, 1685 cm^{-1}.

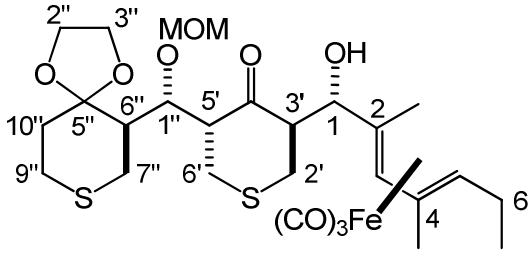
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.90 (1H, s, HC-1), 5.41 (1H, s, HC-2), 2.75 (1H, br dd, *J* = 6, 7 Hz, HC-5), 2.18 (3H, s, H_3CC-4), 2.06-1.98 (1H, m, HC-6), 1.78-1.69 (1H, m, HC-6), 1.17 (3H, t, *J* = 7 Hz, H_3C-7), 1.17 (3H, s, H_3C-2).

^{13}C NMR (125 MHz, $CDCl_3$) δ 198.9 (s, C-1), 107.9 (s, C-4), 89.8 (d, C-3), 69.1 (d, C-5), 62.3 (s, C-2), 24.7 (t, C-6), 19.2 (q, CH_3C-4), 15.6 (q, CH_3C-2), 12.7 (q, C-7).

LRMS (EI), *m/z* (relative intensity): 278 ([M]$^+$, 3), 250 (21), 222 (58), 178 (40), 124 (29), 109 (100), 95 (16), 67 (16).

HRMS (EI), *m/z* calcd for $C_{12}H_{14}FeO_4$: 278.0241; found: 278.0244.

Tricarbonyl[(2,3,4,5-η)-(*S*,2*E*,4*E*)-*rel*-1-((3*R*,5*R*)-tetrahydro-5-((*R*)-(methoxymethoxy)((*R*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)methyl)-3-oxo-2*H*-thiopyran-3-yl)-2,4-dimethylhepta-2,4-dien-1-ol)]iron (141).



141

^{t}BuLi (1.7 M in hexane; 0.25 mL, 0.42 mmol) was slowly added to a solution of **140** (100 mg, 0.29 mmol) in THF (7 mL) at –78 °C. After 30 minutes, a solution of (±)-**138b** (160 mg, 0.57 mmol) in THF (1 mL) was added slowly to the reaction mixture. After 1 h, the reaction was quenched by addition of phosphate buffer (pH 7; 25 mL). The mixture was transferred to an ice bath and vigorously stirred. After 15 min, the mixture

was diluted with CH_2Cl_2, washed with saturated aq NH_4Cl, dried over Na_2SO_4, concentrated, and fractionated by FCC (20% ethylacetate in hexane) to give **142** (18 mg, 10%) and **141** (102 mg, 56%). For each diastereomer, a crystal suitable for X-ray crystallography was obtained on standing from a solution in a 95:5 mixture of hexane and ethyl acetate, respectively.

IR (DRIFT) ν_{max}: 3488, 2033, 1965, 1706 cm^{-1}.

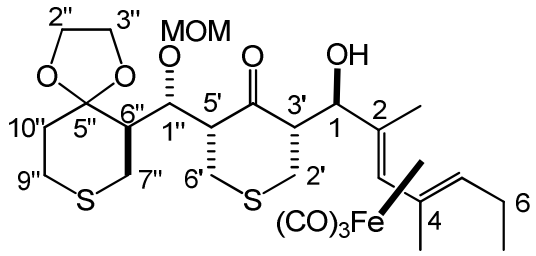
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.40 (1H, s, HC-3), 4.77 (1H, d, *J* = 6.5 Hz, OCHO), 4.75 (1H, dd, *J* = 2.5, 3 Hz, HC-1''), 4.68 (1H, d, *J* = 6.5 Hz, OCHO), 3.99 (1H, dd, *J* = 3.5, 10 Hz, HC-1), 3.99-3.95 (2H, m, HC-2'', HC-3''), 3.80-3.74 (2H, m, HC-2'', HC-3''), 3.54 (1H, ddd, *J* = 2.5, 6, 10 Hz, HC-5'), 3.38 (3H, s, H_3CO), 3.12-3.05 (3H, m, HC-2', H_2C-6'), 2.99 (1H, dd, *J* = 11.5, 13 Hz, HC-7''), 2.91 (1H, ddd, *J* = 3.5, 4, 10 Hz, HC-3'), 2.88-2.80 (3H, m, HC-2', HC-7'', HC-9''), 2.52-2.46 (1H, m, HC-9''), 2.46 (1H, ddd, *J* = 2.5, 3, 11.5 Hz, HC-6''), 2.23 (3H, s, H_3CC-4), 2.22 (1H, dd, *J* = 5.5, 8 Hz, HC-5''), 2.06 (1H, ddd, *J* = 2.5, 4, 13.5 Hz, HC-10''), 1.95 (1H, ddq, *J* = 5.5, 14.5, 7.5 Hz, HC-6), 1.91 (1H, d, *J* = 3.5 Hz, HO), 1.76-1.66 (2H, m, HC-6'', HC-10''), 1.12 (3H, t, *J* = 7 Hz, H_3C-7), 1.11 (3H, s, H_3CC-2).

^{13}C NMR (125 MHz, $CDCl_3$) δ 210.1 (s, C-4'), 108.7 (s, C-5''), 104 (s, C-4), 97.9 (t, OCH_2O), 88.9 (d, C-3), 81.4 (d, C-1), 73.0 (d, C-1''), 70.5 (s, C-2), 68.5 (d, C-5), 64.8 (t, C-2''), 64.3 (t, C-3''), 56.3 (q, CH_3O), 55.5 (d, C-3'), 53.5 (d, C-5'), 51.0 (d, C-6''), 37.3 (t, C-10''), 32.0 (t, C-6''), 31.7 (t, C-2''), 28.7 (t, C-7''), 27 (t, C-9''), 24.7 (t, C-6), 19.7 (q, CH_3C-4), 15.7 (q, CH_3C-2), 13.7 (q, C-7).

LRMS (ESI), *m/z* (relative intensity): 649 ([M+23]$^+$, 7), 579 (6), 468 (10), 371 (97), 301 (100), 279 (7), 206 (5).

HRMS (ESI), *m/z* calcd for $C_{27}H_{38}FeO_9S_2$+Na: 649.1204; found: 649.1225.

Tricarbonyl[(2,3,4,5-η)-(*R*,2*E*,4*E*)-*rel*-1-((3*S*,5*R*)-tetrahydro-5-((*R*)-(methoxymethoxy)((*R*)-1,4-dioxa-8-thiaspiro[4.5]decan-6-yl)methyl)-3-oxo-2*H*-thiopyran-3-yl)-2,4-dimethylhepta-2,4-dien-1-ol)]iron (142).

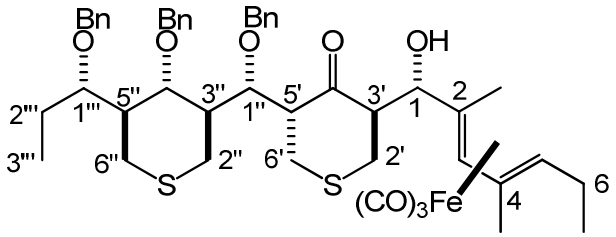


142

pale yellow crystalline solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.92 (1H, s), 4.81 (1H, t, *J* = 2.5 Hz), 4.70 (1H, d, *J* = 6.5 Hz), 4.63 (1H, d, *J* = 6.5 Hz), 3.95 (1H, ddd), 3.82 (2H, ap t, *J* = 7 Hz), 3.75-3.70 (1H, m), 3.53-3.49 (2H, m), 3.36 (3H, s), 3.01-2.74 (10H, m), 2.49 (1H, ddd, *J* = 2, 3, 13 Hz), 2.40 (1H, ddd, *J* = 3, 3, 12 Hz), 2.16 (3H, s), 2.04 (1H, ddd, *J* = 3, 4, 13 Hz), 1.95-1.89 (1H, m), 1.74-1.61 (2H, m), 1.13 (3H, s), 1.09 (3H, t, *J* = 7.5 Hz).

Tricarbonyl[(2,3,4,5-η)-(*S*,2*E*,4*E*)-*rel*-1-((3*R*,5*R*)-5-((*S*)-benzyloxy((3*S*,4*S*,5*S*)-4-(benzyloxy)-5-((*S*)-1-(benzyloxy)propyl)tetrahydro-2*H*-thiopyran-3-yl)methyl)-4-oxotetrahydro-2*H*-thiopyran-3-yl)-2,4-dimethylhepta-2,4-dien-1-ol)]iron (143).



143

^{t}BuLi (1.7 M in hexane; 80 μL, 0.14 mmol) in hexane was added slowly to a solution of **129** (53 mg, 0.09 mmol, 0.02 M) in THF (4.5 mL) at –78 °C. After 30 min, a solution of (±)-**138b** (49 mg, 0.18 mmol) in THF (1 mL) was added to the reaction mixture. After 3 h, the reaction was quenched by addition of phosphate buffer (pH 7; 2 mL). The mixture was transferred to an ice bath and vigorously stirred. After 15 min, the mixture was diluted with CH_2Cl_2, washed with saturated aq NH_4Cl, dried over Na_2SO_4, concentrated, and fractionated by FCC (10% acetone in pentane) to give the titled compound as an inseparable 5:1 mixture of two diastereomers (64 mg, 82%) as a plae yellow oil.

IR (DRIFT) ν_{max}: 3541, 2037, 1968, 1703 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.27 (15H, m, Ph), 5.14 (1H, s, HC-3'), 4.71 and 4.55 (2H, d ×2, *J* = 11.5 Hz, H_2CPh), 4.65 and 4.41 (2H, d ×2, *J* = 11.5 Hz, H_2CPh), 4.50 and 4.38 (2H, d ×2, *J* = 10.5 Hz, H_2CPh), 4.57 (1H, br d, *J* = 7 Hz, HC-1''), 3.76 (1H, dd, *J* = 3, 9.5 Hz, HC-1), 3.70-3.65 (1H, m, HC-1'''), 3.33-3.24 (2H, m, HC-4'', HC-5'), 3.14 (1H, ddd, *J* = 4.5, 7, 9.5 Hz, HC-3'), 3.10-3.05 (2H, m, H_2C-6'), 2.94 (1H, dd, *J* = 4.5,

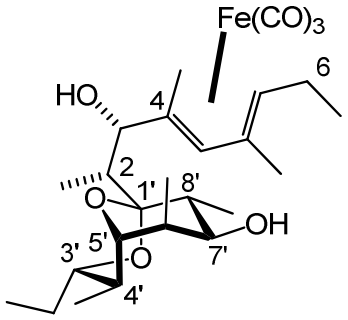
13.5 Hz, HC-2'), 2.92-2.79 (2H, m, HC-2'', HC-6''), 2.74 (1H, dd, *J* = 7, 13.5 Hz, HC-2'), 2.63 (1H, dd, *J* = 11.5, 13.5 Hz, HC-2'' or HC-6''), 2.55-2.39 (3H, m, HC-3'', HC-5'', HC-2'' or HC-6''), 2.24 (1H, d, *J* = 3 Hz, HO), 2.20 (3H, s, H_3CC-4), 2.11 (1H, dd, *J* = 6, 8 Hz, HC-5), 1.98-1.89 (1H, m, HC-6), 1.71-1.59 (2H, m, HC-2''', HC-6), 1.39 (1H, ddq, *J* = 10.5, 14, 7 Hz, HC-2'''), 1.10 (3H, t, *J* = 7 Hz, H_3C-7), 0.97 (3H, t, *J* = 7 Hz, H_3C-1'''), 0.92 (3H, s).

^{13}C NMR (125 MHz, $CDCl_3$) δ 211.6 (s, C-4'), 138.9 (s, Ph), 138.2 (s, Ph), 138.0 (s, Ph), 128.65 (d ×2, Ph), 128.64 (d ×2, Ph), 128.53 (d ×2, Ph), 128.2 (d ×2, Ph), 128.13 (d ×2, Ph), 128.03 (d, Ph), 127.96 (d ×2, Ph), 127.9 (d, Ph), 127.8 (d, Ph), 103.6 (s, C-4), 88.9 (d, C-3), 81.4 (d, C-1), 80.1 (d, C-1'''), 77.8 (d, C-4''), 76.2 (d, C-1''), 73.6 (t, CH_2Ph), 71.6 (t, CH_2Ph), 70.3 (s, C-2), 69.7 (t, CH_2Ph), 68.0 (d, C-5), 55.5 (d, C-3'), 54.3 (d, C-5'), 48.5 (d, C-3'' or C-5''), 47.4 (d, C-3'' or C-5''), 35.5 (t, C-6'), 33.4 (t, C-2'), 29.7 (t, C-2'' or C-6''), 27.8 (t, C-2'' or C-6''), 24.7 (t, C-6), 22.7 (t, C-2'''), 19.6 (q, CH_3C-4), 15.7 (q, C-7), 13.7 (q, CH_3C-2), 11.6 (q, C-3'').

LRMS (ESI), *m/z* (relative intensity): 891 ($[M+23]^+$, 3), 613 (3), 465 (1), 383 (2), 311 (100), 215 (3), 127 (6).

HRMS (ESI), *m/z* calcd for $C_{47}H_{56}FeO_8S_2$+Na: 891.2658; found: 891.2675.

Tricarbonyl[(4,5,6,7-η)-(2*R*,3*S*,4*E*,6*E*)-*rel*-2-((1*S*,3*S*,4*S*,5*R*,6*R*,7*S*,8*R*)-3-ethyl-7-hydroxy-4,6,8-trimethyl-2,9-dioxabicyclo[3.3.1]nonan-1-yl)-4,6-dimethylhepta-4,6-dien-3-ol)]iron (145).



145

A suspension of Raney nickel (W2), previously deactivated by refluxing in acetone for 15 min; 7 mL settled volume) in EtOH (8 mL) was added to **143** (50 mg, 0.06 mmol) and the mixture was heated under reflux with vigorous stirring. After 2 h (reaction was complete by TLC analysis), the mixture was decanted and the solid was suspended in EtOH (8 mL) and heated under reflux with vigorous stirring for several min. This washing procedure was repeated using acetone and methanol. The combined organic layers were filtered through Celite®, concentrated, and fractionated by FCC (10% acetone in pentane) to give the titled compound (12 mg, 40%) as a pale yellow oil.

IR (DRIFT) ν_{max}: 3477, 2033, 1967, 1950, 1634 cm^{-1}.

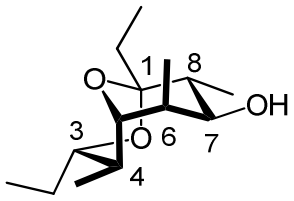
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.05 (1H, s, HC-5), 4.19 (1H, s, HOC-3), 3.90 (1H, dd, *J* = 5, 10 Hz, HC-7'), 3.57 (1H, br s, HC-5'), 3.49 (1H, ddd, *J* = 3.5, 6, 9.5 Hz, HC-3'), 3.46 (1H, br d, *J* = 8.5 Hz, HC-3), 2.17 (3H, s, H_3CC-6), 2.16-2.12 (2H, m, HC-2, HC-7), 1.96-1.80 (3H, m, HC-6', HC-8', HC-8), 1.72-1.63 (3H, m, HC-1'', HC-4', HC-8), 1.49-1.41 (1H, m, HC-1''), 1.12 (3H, s, H_3CC-6), 1.08 (3H, t, *J* = 7.5 Hz, H_3C-9), 1.07 (3H, d,

J = 7 Hz, H_3CC-6 or H_3CC-8'), 1.04 (3H, d, *J* = 6.5 Hz), 0.93 (3H, t, *J* = 7.5 Hz, H_3C-2"), 0.91 (6H, br d, *J* = 7 Hz, H_3CC-4', H_3C-8).

^{13}C NMR (125 MHz, C_6D_6) δ 105.0, 103.1, 90.6, 82.7, 81.3, 75.1, 73.2, 69.2, 66.4, 44.7, 39.9, 38.5, 38.3, 26.7, 25.2, 19.4, 18.9, 16.1, 14.9, 12.8, 11.9, 11.5, 9.5.

HRMS *m/z* calcd for $C_{26}H_{40}O_7Fe$+Na: 543.2015; found: 543.2002 (ESI).

(1*S*,3*S*,4*S*,5*R*,6*R*,7*S*,8*R*)-1,3-Diethyl-4,6,8-trimethyl-2,9-dioxabicyclo[3.3.1]nonan-7-ol (151a).



151a

A suspension of Raney nickel (W2; 20 mL settled volume) in THF (60 mL) was added to **121** (200 mg, 0.548 mmol) and the mixture was heated under reflux with vigorous stirring. After 15 min, the mixture was decanted and the solid was suspended in THF (60 mL) and heated under reflux with rapid stirring for several min. This washing procedure was repeated once by EtOH, MeOH, and ethyl acetate. The combined organic layers were filter through Celite® and concentrated. The residue was dissolved in a 5:1 mixture (*v/v*) of THF and H_2O respectively (9 mL) and aq HCl (10 M; 1 mL). After 2 h, the reaction mixture was cooled to 0 °C and neutralized with saturated aq $NaHCO_3$. The mixture was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (50% ethyl acetate in hexane) to give the titled compound (110 mg, 83%).

IR (DRIFT) ν_{max}: 3396 cm^{-1}.

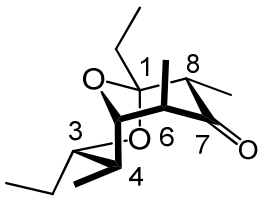
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.95 (1H, ddd, *J* = 5, 5, 10 Hz, HC-7), 3.49 (1H, dd, *J* = 3.5,1.5 Hz, HC-5), 3.34 (1H, ddd, *J* = 2.5, 8, 10.5 Hz, HC-3), 1.85 (1H, ddq, *J* = 1.5, 7, 7 Hz, HC-6), 1.72-1.49 (5H, m, H_2C-1, HCC-3,HC-4, HC-8), 1.38 (1H, br s, HO), 1.33 (1H, ddq, *J* = 8, 14, 7.5 Hz, HCC-3), 1.07 (3H, d, *J* = 7 Hz, H_3CC-6), 1.00 (3H, d, *J* = 6.5 Hz, H_3CC-8), 0.93 (3H, t, *J* = 7.5 Hz, H_3CCC-3), 0.91 (3H, d, *J* = 7 Hz, H_3CC-4), 0.91 (3H, t, *J* = 7.5 Hz, H_3CCC-1).

^{13}C NMR (125 MHz, $CDCl_3$) δ 101.8 (s, C-1), 81.5 (d, C-5), 73.6 (d, C-3), 70.2 (d, C-7), 39.64 (d, C-4 or C-6), 39.60 (d, C-4 or C-6), 39.2 (d, C-8), 30.5 (t, CH_2C-1), 25.6 (t, CH_2C-3), 18.4 (q, CH_3C-4), 12.0 (q, CH_3C-6), 11.1 (q, CH_3C-8), 9.6 (q, CH_3CC-3), 7.5 (q, CH_3CC-1).

LRMS (EI), *m/z* (relative intensity): 242 ($[M]^+$, 1), 126 (12), 115 (46), 110 (100), 95 (29), 69 (36), 57 (83).

HRMS (EI), *m/z* calcd for $C_{14}H_{26}O_3$: 243.1882; found: 242.1886.

(1*S*,3*S*,4*S*,5*S*,6*S*,8*R*)-1,3-Diethyl-4,6,8-trimethyl-2,9-dioxabicyclo[3.3.1]nonan-7-one (152).



152

IBX (25 mg, 0.09 mmol) was added to a stirred solution of **151a** (20 mg, 0.08 mmol) in DMSO (0.8 mL) and THF (0.4 mL) at ambient temperature. After 2 h (reaction was complete by TLC analysis), the mixture was diluted with ethyl acetate and washed with saturated aq $NaHCO_3$, dried over Na_2SO_4, concentrated, and fractionated by PTLC (10% ethyl acetate in hexane) to give the titled compound (15 mg, 76%).

IR (DRIFT) ν_{max}: 2966, 2933, 2878, 1719, 1457, 1206 cm^{-1}.

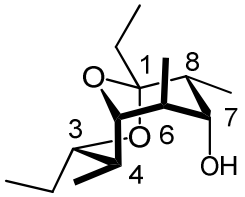
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.64 (1H, br d, *J* = 3 Hz, HC-5), 3.30 (1H, ddd, *J* = 2, 8.5, 9.5 Hz, HC-3), 2.77 (1H, q, *J* = 6.5 Hz, HC-8), 2.37 (1H, q, *J* = 7 Hz, HC-6), 1.80 (1H, dq, *J* = 14, 7.5 Hz, HCC-1), 1.62 (1H, dq, *J* = 14, 7.5 Hz, HCC-1), 1.57 (1H, ddq, *J* = 2.5,14, 7.5 Hz, HCC-3), 1.42 (1H, ddq, *J* = 3, 9.5, 7 Hz, HC-4), 1.30 (3H, d, *J* = 7 Hz, H_3CC-6), 1.28-1.19 (1H, m, *J* = 8.5, 14, 7 Hz, HCC-3), 1.03 (3H, d, *J* = 7 Hz, H_3CC-8), 0.99 (3H, t, *J* = 7.5 Hz, H_3CCC-1), 0.91 (3H, d, *J* = 7 Hz, H_3CC-4), 0.86 (3H, t, *J* = 7.5 Hz, H_3CCC-3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 211.9 (s, C-7), 104.6 (s, C-1), 82.2 (d, C-5), 73.5 (d, C-3), 51.3 (d, C-6), 48.3 (d, C-8), 41.5 (d, C-4), 30.1 (t, CH_2C-1), 25.6 (t, CH_2C-3), 17.9 (q, CH_3C-6), 17.6 (q, CH_3C-4), 9.7 (q, CH_3CC-3), 8.0 (q, CH_3C-8 or CH_3CC-1), 7.9 (q, CH_3C-8 or CH_3CC-1).

LRMS (EI), *m/z* (relative intensity): 240 ($[M]^+$, 29), 153 (6), 149 (12), 137 (12), 113 (53), 110 (26), 95 (26), 69 (41), 57 (100), 55 (16).

HRMS (EI), *m/z* calcd for $C_{14}H_{24}O_3$: 240.1725; found: 240.1727.

(1*S*,3*S*,4*S*,5*R*,6*R*,7*R*,8*R*)-1,3-Diethyl-4,6,8-trimethyl-2,9-dioxabicyclo[3.3.1]nonan-7-ol (151b).



151b

$NaBH_4$ (10 mg, 0.26 mmol) was added to a solution of **152** (15 mg, 0.06 mmol) in methanol (2 mL) at ambient temperature. After 45 minutes (reaction was complete by TLC analysis), the mixture was diluted with CH_2Cl_2 (10 mL), washed with water, dried over Na_2SO_4, and concentrated to give the titled compound (12 mg, 79%).

IR (DRIFT) ν_{max}: 3520 cm^{-1}.

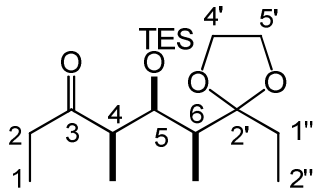
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.14 (1H, br s, HO), 3.51 (1H, br s, HC-7), 3.46 (1H, br s, HC-5), 3.40 (1H, br dd, *J* = 9,10 Hz, HC-3), 2.15 (1H, ddq, *J* = 2, 10, 7 Hz, HC-4), 2.02 (1H, br q, *J* = 7 Hz, HC-6), 1.97 (1H, dq, *J* = 3.5, 7 Hz, HC-8), 1.73-1.54 (3H, m, H_2CC-1' HCC-3), 1.31 (1H, ddq, *J* = 9, 14, 7.5 Hz, HCC-3), 1.08 (3H, d, *J* = 7 Hz, H_3CC-6), 1.07 (3H, d, *J* = 7 Hz, H_3CC-8), 0.95 (3H, t, *J* = 7.5 Hz, H_3CCC-3), 0.93 (3H, d, *J* = 7 Hz, H_3CC-4), 0.92 (3H, t, *J* = 7.5 Hz, H_3CCC-1).

^{13}C NMR (125 MHz, $CDCl_3$) δ 103.1 (s, C-1), 80.6 (d, C-5), 76.2 (d, C-7), 75.1 (d, C-3), 41.1 (d, C-6), 40.7 (d, C-4), 33.9 (d, C-8), 29.4 (t, CH_2C-1), 26.4 (t, CH_2C-3), 18.9 (q, CH_3C-4 or CH_3C-6), 18.7 (q, CH_3C-4 or CH_3C-6), 12.4 (q, CH_3C-8), 10.2 (q, CH_3CC-3), 7.6 (q, CH_3CC-1).

LRMS (CI, NH_3), *m/z* (relative intensity): 243 ($[M+1]^+$, 100), 225 (11), 110 (29), 64 (100), 95 (32), 69 (50), 57 (100), 55 (18).

HRMS (CI, NH_3), *m/z* calcd for $C_{14}H_{26}O_3$+H: 243.1983; found: 243.1960.

(4R,5R,6S)-6-(2-Ethyl-1,3-dioxolan-2-yl)-4-methyl-5-((triethylsilyl)oxy)heptan-3-one (164).



(-)-164

A suspension of Raney nickel (W2; 70 mL settled volume) in EtOH (150 mL) was added to (+)-***O*-TES-9a** (4.90 g, 11.7 mmol) and the mixture was heated under reflux with vigorous stirring. After 2 h (reaction was complete by TLC analysis), the mixture was decanted and the solid was suspended in EtOH (200 mL) and heated under reflux with vigorous stirring for several min. This washing procedure was repeated twice with acetone, and twice with methanol. The combined organic layers were filtered through Celite®, concentrated, and fractionated by FCC (10% ethyl acetate in hexane) to give the titled compound (3.28 g, 78%): $[\alpha]_D$ -60 (*c* 1.0, $CHCl_3$).

IR (DRIFT) ν_{max}: 1710 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.15 (1H, br dd, *J* = 3, 4 Hz, HC-5), 3.95-3.87 (4H, m, H_2C-4', H_2C-5'), 2.75 (1H, dq, *J* = 4, 6.5 Hz, HC-4), 2.64 (1H, dq, *J* = 18, 7 Hz, HC-2), 2.41 (1H, dq, *J* = 18, 7 Hz, HC-2), 1.85 (1H, dq, *J* = 3, 7 Hz, HC-6), 1.68 (1H, dq, *J* =

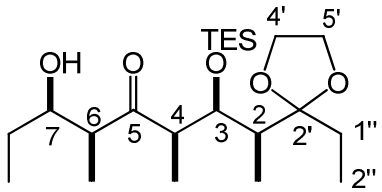
14.5, 7.5 Hz, HC-1"), 1.59 (1H, dq, *J* = 14.5, 7.5 Hz, HC-1"), 1.03 (3H, d, *J* = 6.5 Hz, H_3CC-4), 1.02 (3H, t, *J* = 7.5 Hz, H_3C-1), 0.96 (9H, t, *J* = 8 Hz, H_3CCCSi ×3), 0.84 (3H, t, *J* = 7 Hz, H_3C-2"), 0.83 (3H, d, *J* = 7 Hz, H_3CC-6), 0.62 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 214.1 (s, C-3), 113.8 (s, C-2'), 72.9 (d, C-5), 65.2 (t, C-4'), 65.1 (t, C-5'), 52.7 (d, C-4), 41.9 (d, C-6), 36.4 (t, C-2), 26.9 (t, C-1"), 12.5 (q, CH_3C-4), 10.6 (q, CH_3C-6), 7.8 (q, C-2"), 7.4 (q, C-1), 7.3 (q ×3, CH_3CSi), 5.6 (t ×3, CH_2Si).

LRMS (CI, NH_3), *m/z* (relative intensity): 359 ($[M+1]^+$, 0.5), 329 (2), 273 (2), 227 (8), 101 (100), 57 (2).

HRMS *m/z* calcd for $C_{19}H_{38}O_4Si$+H: 359.2618; found: 359.2611 (CI, NH_3).

(2S,3R,4R,6S,7R)-2-(2-Ethyl-1,3-dioxolan-2-yl)-7-hydroxy-4,6-dimethyl-3-(triethylsilyloxy)nonan-5-one (165).



(+)-165

A solution of (-)-**164** (3.61 g, 10.1 mmol) in Et_2O (15 mL) was added dropwise via syringe to a stirred solution of Et_3N (3.1 mL, 2.2 g, 22 mmol) and 9-BBN-OTf (0.5 M in hexane; 40 mL, 20 mmol) in Et_2O (220 mL) at −78 °C under argon. After 2 h, a solution of propanal (3.6 mL, 2.9 g, 50 mmol) in Et_2O (30 mL) was slowly added via syringe. After 4 h, the reaction was quenched by sequential addition of MeOH (90 mL),

phosphate buffer (pH 7; 300 mL), and 30% aqueous H_2O_2 (90 mL). The reaction vessel was transferred to an ice bath and after vigorous stirring for 20 min, the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated to give the crude product whose ^{1}H NMR spectrum indicated the presence of 2.4:1 mixture of a single adduct (>20:1 dr) and (-)-**164**, respectively. Fractionation of the crude by FCC (20% ethyl acetate in hexane) gave recovered (-)-**164** (0.80 g, 22%) and the titled compound (2.6 g, 62%): $[\alpha]_D$ +92 (*c* 1.7, $CHCl_3$).

IR (DRIFT) ν_{max} 3510, 1696, 2878 cm^{-1}.

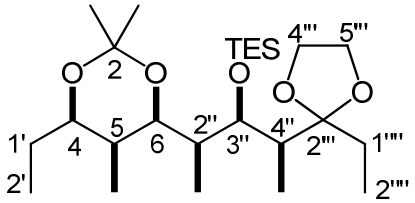
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.09 (1H, dd, *J* = 3, 4.5 Hz, HC-3), 3.94-3.85 (5H, m, H_2C-4', H_2C-5', HC-7), 3.29 (1H, br d, *J* = 1.5 Hz, HOC-3), 2.99 (1H, dq, *J* = 4.5, 7 Hz, HC-4), 2.82 (1H, dq, *J* = 2, 7.5 Hz, HC-6), 1.91 (1H, dq, *J* = 3, 7 Hz, HC-2), 1.66 (1H, dq, *J* = 14.5, 7.5 Hz, HC-1''), 1.61-1.51 (2H, m, HC-1'', HC-8), 1.10 (3H, d, *J* = 7.5 Hz, H_3CC-6), 1.01 (3H, d, *J* = 7 Hz, H_3CC-4), 0.96 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.93 (3H, d, *J* = 7.5 Hz, H_3C-9), 0.84 (3H, t, *J* = 7.5 Hz, H_3C-2''), 0.82 (3H, d, *J* = 7 Hz, H_3C-1), 0.62 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 220.3 (s, C-5), 113.7 (s, C-2'), 73.0 (d, C-3), 72.2 (d, C-7), 65.1 (t, C-4'), 65.0 (t, C5'), 51.3 (d, C-4), 49.3 (d, C-6), 41.2 (d, C-2), 26.9 (t, C-1''), 26.7 (t, C-8), 13.0 (q, CH_3C-4), 10.6 (q, C-1 or C-9), 10.5 (q, C-1 or C-9), 9.3 (q, CH_3C-6), 7.5 (q, C-2''), 7.2 (q ×3, CH_3CSi), 5.5 (t ×3, CH_2Si).

LRMS (CI, NH_3), *m/z* (relative intensity): 417 ($[M+1]^+$, 6), 387 (20), 355 (30), 329 (30), 297 (23), 229 (13), 199 (10), 165 (6), 101 (100).

HRMS (CI, NH_3), *m/z* calcd for $C_{22}H_{44}O_5Si$+H: 417.3036; found: 417.3040.

(4*R*,5*S*,6*R*)-4-Ethyl-6-[(2*R*,3*R*,4*S*)-4-(2-ethyl-1,3-dioxolan-2-yl)-3-(trimethylsilyl)oxypentan-2-yl]-2,2,5-trimethyl-1,3-dioxane (167).



167

A solution of (+)-**165** (20 mg, 0.048 mmol) in THF (2 ml) was added dropwise via syringe to a stirred suspension of $LiAlH_4$ (3.5 mg, 0.09 mmol) in THF (3 mL) at 0 °C. After 15 min, H_2O (0.3 mL), and 15% aq NaOH (0.3 mL) were sequentially added to the reaction mixture at 0 °C [Caution: H_2 evolution]. After 5 min, the reaction mixture was diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4, and concentrated to give the crude product (12 mg). The crude mixture was taken up in CH_2Cl_2 (1 mL) and 2,2-dimethoxypropane (0.5 mL) and *p*-TsOH·H_2O (2 mg, 0.01 mmol) were sequentially added to the stirred solution. After 5 min, the mixture was diluted with CH_2Cl_2 and washed with saturated aq $NaHCO_3$, dried over Na_2SO_4, concentrated, and fractionated by PTLC (15% ethylacetate in hexane) to give the titled compound (10 mg, 43%).

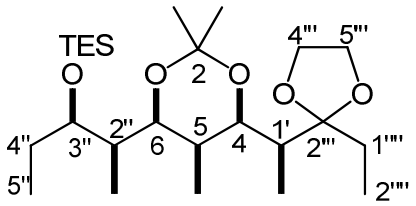
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.95-3.88 (5H, m, HC-3'', H_2C-4''', H_2C-5'''), 3.73 (1H, ddd, *J* = 2, 7, 7 Hz, HC-4), 3.64 (1H, dd, *J* = 2. 9.5 Hz, HC-6), 1.97 (1H, dq, *J* = 4.5, 7 Hz, HC-4''), 1.70 (1H, ddq, *J* = 1.5, 9.5, 6.5 Hz, HC-2''), 1.67-1.52 (4H, m, HC-1', H_2C-1'''', HC-5), 1.47-1.39 (1H, m, HC-1'), 0.98 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.93 (3H, d, *J* = 7 Hz, H_3C-5''), 0.90 (3H, d, *J* = 6.5 Hz, H_3C-1''), 0.89 (3H, t, *J* = 7 Hz, H_3C-2'), 0.87 (3H, d, *J* = 6.5 Hz, H_3CC-5), 0.85 (3H, t, *J* = 7.5 Hz, H_3C-1''''), 0.67-0.54 (6H, m, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 114.3 (s), 99.1 (s), 75.3 (d), 75.2 (d), 69.3 (d), 65.0 (t), 64.8 (t), 43.1 (d), 42.6 (d), 32.1 (d), 30.3 (q, CH_3C-2), 26.6 (t), 25.7 (t), 20.0 (q, CH_3C-2), 12.3 (q), 9.8 (q), 9.3 (q), 7.7 (q), 7.4 (q), 6.0 (t ×3), 4.7 (q ×3).

LRMS (CI, NH_3), *m/z* (relative intensity): 459 ($[M+1]^+$, 3), 401 (8), 327 (22), 215 (9), 157 (22), 132 (10), 101 (100).

HRMS (CI, NH_3), *m/z* calcd for $C_{25}H_{50}O_5Si$+H: 459.3506; found: 459.3495.

4*R*,5*S*,6*R*)-4-[(*S*)-1-(2-Ethyl-1,3-dioxolan-2-yl)ethyl]-6-[(2*S*,3*R*)-3-(trimethylsilyl)oxypentan-2-yl]-2,2,5-trimethyl-1,3-dioxane (169).



169

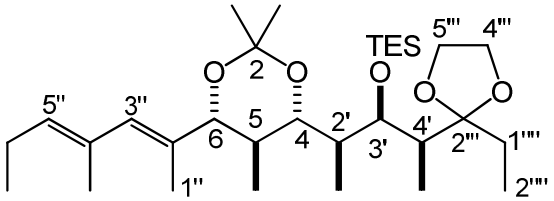
A solution of (+)-**165** (20 mg, 0.048 mmol) in THF (2 ml) was added dropwise via syringe to a stirred suspension of $LiAlH_4$ (3.5 mg, 0.09 mmol) in THF (3 mL) at 0 °C. After 15 min, H_2O (0.3 mL), and 15% aq NaOH (0.3 mL) were sequentially added to the reaction mixture at 0 °C [Caution: H_2 evolution]. After 5 min, the reaction mixture was diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4, and concentrated to give the crude product (12 mg). TBAF (20 mg, 0.08 mmol) was added to a stirred solution of the above crude product in THF (2 mL) at ambient temperature. After 2 h, the reaction mixture diluted with CH_2Cl_2, washed with saturated aq NH_4Cl, dried over Na_2SO_4, concentrated, and fractionated by PTLC (20% ether in dichloromethane) to give a crude

triol (7.2 mg). TESOTf (6.0 µL, 7.0 mg 0.03 mmol) and 2,6 lutidine (6 µl, 5.5 mg, 0.05 mmol) were added sequentially to a solution of the crude triol (7.2 mg, 0.02 mmol) in CH_2Cl_2 (1 mL) at 0 °C under argon. After 1 h, the reaction mixture was diluted with CH_2Cl_2, washed with saturated aq $NaHCO_3$, dried over Na_2SO_4, concentrated, and fractionated by PTLC (20% ethyl acetate in hexane) to give the mono-silyl protected diol (8 mg, 40% from (+)-**165**). 2,2-dimethoxypropane (0.5 mL) and *p*-TsOH·H_2O (2 mg, 0.01 mmol) were sequentially added to a solution of the above mono-silyl protected diol (8.0 mg, 0.02 mmol) in CH_2Cl_2 (1 mL). After 5 min, the reaction mixture was diluted with CH_2Cl_2, and washed with saturated aq $NaHCO_3$, dried over Na_2SO_4, concentrated, and fractionated by PTLC (15% ethyl acetate in hexane) to give the titled compound (8 mg, 91%; 36% from (+)-**165**).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.94-3.88 (4H, m, H_2C-4''', HC-5'''), 3.82 (1H, dd, *J* = 2, 6.5 Hz, HC-4), 3.71 (1H, dd, *J* = 1.5, 9.5 Hz, HC-6), 3.64 (1H, br ddd, *J* = 1.5, 7, 7.5 Hz, HC-3''), 1.87 (1H, dq, *J* = 6.5, 7 Hz, HC-1'), 1.79 (1H, ddq, *J* = 1.5, 2, 6.5 Hz, HC-5), 1.74 (1H, dq, *J* = 14, 7.5 Hz, HC-1''''), 1.64 (1H, ddq, *J* = 1.5, 9.5, 6.5 Hz, HC-2''), 1.57 (1H, dq, *J* = 14, 7.5 Hz, HC-1''''), 1.56-1.46 (2H, m, H_2C-4''), 1.37 (6H, s, H_3CC-2 ×2), 0.98 (3H, d, *J* = 7 Hz, H_3C-2'), 0.96 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.87 (3H, d, *J* = 6.5 Hz, H_3C-1''), 0.86 (3H, d, *J* = 6.5 Hz, H_3CC-5), 0.86 (3H, t, *J* = 7.5 Hz, H_3C-2''''), 0.81 (3H, t, *J* = 7.5 Hz, H_3C-5''), 0.64-0.52 (6H, m, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 113.6 (s), 99.0 (s), 75.9 (d), 73.8 (d), 72.4 (d), 65.5 (t), 65.1 (t), 42.3 (d), 36.9 (d), 34.1 (d), 30.3 (q, CH_3C-2), 28.3 (t), 25.7 (t), 19.7 (q, CH_3C-2), 12.3 (q), 10.4 (q), 8.6 (q), 7.3 (q), 6.8 (q), 6.3 (q ×3), 5.8 (t ×3).

(4*R*,5*R*,6*R*)-4-[(2*R*,3*R*,4*S*)-4-(2-Ethyl-1,3-dioxolan-2-yl)-3-(triethylsilyloxy)pentan-2-yl]-2,2,5-trimethyl-6-[(2*E*,4*E*)-4-methylhepta-2,4-dien-2-yl]-1,3-dioxane (172).



172

(*c*-Hex)$_2$BCl (1 M in hexane; 280 µL, 0.280 mmol) and Et_3N (0.040 mL, 29 mg, 0.29 mmol) were sequentially added via syringe in to a solution of (-)-**164** (50 mg, 0.14 mmol) in Et_2O (1.4 mL) at 0 °C under argon. After 1 h, the mixture was cooled to –78 °C and after 10 min, the dienealdehyde **73** (38 mg, 0.27 mmol) was added dropwise via syringe. After 4 h, the reaction was quenched by sequential addition of MeOH (1 mL), phosphate buffer (pH 7; 2 mL), and 30% aqueous H_2O_2 (0.6 mL). The reaction vessel was transferred to an ice bath and after vigorously stirring for 15 min, the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (10% ethyl acetate in hexane) to give an aldol adduct (30 mg, 42%; dr >10). DIBAL-H (1 M in toluene; 30 µL, 0.030 mmol) was added to a solution of the above aldol adduct (10 mg, 0.02 mmol) in THF (1 mL) at –78 °C. The mixture was allowed to warm to 0 °C and after 5 min, was diluted with ethyl acetate, washed sequentially with water and brine, dried over Na_2SO_4, concentrated, and fractionated by PTLC (10% ethyl acetate in hexane) to give the desired 1,3-*syn* diol (5.7 mg, 57%). 2,2-Dimethoxypropane (0.5 mL) and *p*-TsOH·H_2O (1.2 mg, 6.9 µmol) were added to a solution of the above diol (5.7 mg, 0.011 mmol) in CH_2Cl_2 (1 mL). After 5 minutes, the reaction mixture was diluted with CH_2Cl_2, washed with saturated aq

$NaHCO_3$, dried over Na_2SO_4, concentrated, and fractionated by PTLC (10% ethyl acetate in hexane) to give the titled compound (5.2 mg, 85%).

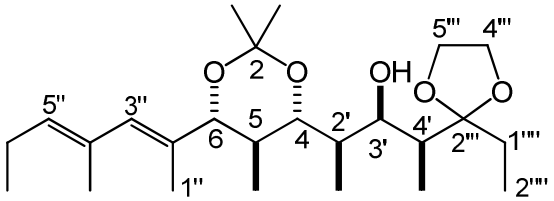
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (1H, s, HC-3''), 5.35 (1H, dd, *J* = 3, 4 Hz, HC-5''), 4.20 (1H, dd, *J* = 4, 3 Hz, HC-3'), 3.94-3.88 (4H, m, H_2C-4'', H_2C-5'''), 3.76 (1H, d, *J* = 10 Hz, HC-6), 3.43 (1H, dd, *J* = 10.5, 3 Hz, HC-4), 2.11-2.05 (2H, m, H_2C-6''), 1.89-1.81 (3H, m, HC-2', HC-4', HC-5), 1.79 (3H, s, H_3C-1''), 1.73 (3H, s, H_3CC-4''), 1.68 (2H, q, *J* = 7 Hz, H_2C-1''''), 1.44 (3H, s, H_3CC-2), 1.39 (3H, s, H_3CC-2), 0.98 (3H, t, *J* = 7.5 Hz, H_3C-7''), 0.96 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.95 (3H, d, *J* = 7 Hz, H_3C-5'), 0.92 (3H, d, *J* = 7 Hz, H_3C-1'), 0.86 (3H, t, *J* = 7.5 Hz, H_3C-2''''), 0.71 (3H, d, *J* = 7 Hz, H_3CC-5), 0.67 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 133.9 (d, HC-3''), 133.0 (d, HC-5''), 132.9 (s, C-2'' or C-4''), 131.7 (s, C-2'' or C-4''), 114.3 (s, C-2'''), 98.1 (s, C-2), 83.3 (d, C-6), 77.9 (d, C-4), 69.9 (d, C-3'), 65.2 (t, C-4'''), 65.0 (t, C-4'''), 45.3 (d, C-4'), 43.0 (d, C-2'), 32.9 (d, C-5), 30.4 (q, H_3CC-2), 27.2 (t, H_2C-1''''), 21.6 (t, H_2C-6''), 20.0 (q, H_3CC-2), 16.9 (q, CH_3C-4''), 14.3 (q, C-7''), 13.9 (q, C-1'), 13.4 (q, CH_3C-5), 13.1 (q, C-1''), 10.4 (q, C-5'), 7.6 (q, C-2''''), 7.4 (t 3, CH_2Si ×3), 5.7 (q ×3, CH_3CSi ×3).

LRMS (ESI), *m/z* (relative intensity): 561 ($[M+23]^+$, 35), 501 (20), 427 (100), 351 (12).

HRMS (ESI), *m/z* calcd for $C_{31}H_{58}O_5Si$+Na: 561.3945; found: 561.3965.

(4*R*,5*R*,6*R*)-4-[(2*R*,3*R*,4*S*)-4-(2-Ethyl-1,3-dioxolan-2-yl)-3-(hydroxyoxy)pentan-2-yl]-2,2,5-trimethyl-6-[(2*E*,4*E*)-4-methylhepta-2,4-dien-2-yl]-1,3-dioxane (173).



173

TBAF (60 mg, 0.23 mmol) was added to a stirred solution of **172** (9.7 mg, 0.18 mmol) in THF (2 mL) at ambient temperature. After 2 days (reaction was complete by TLC analysis), the mixture was diluted with CH_2Cl_2, washed with saturated aq NH_4Cl, dried over Na_2SO_4, concentrated, and fractionated by PTLC (10% ethyl acetate in hexane) to give the titled compound (7.2 mg, 94%).

^{1}H NMR (500 MHz, C_6D_6) δ 5.93 (1H, s, HC-3''), 5.39 (1H, br dd, *J* = 7, 7 Hz, HC-5''), 4.42 (1H, dd, *J* = 1.5, 6 Hz, HC-3'), 3.82 (1H, d, *J* = 10 Hz, HC-6), 3.61 (1H, s, HO), 3.55-3.49 (5H, m, H_2C-4''', H_2C-5''', HC-4 [NOE on irradiation of H_3C-1']), 2.30 (1H, ddq, *J* = 1.5, 2, 7 Hz, HC-2' [NOE on irradiation of H_3CC-5]), 2.15 (1H, ddq, *J* = 10,10, 6.5 Hz, HC-5), 2.11 (1H, dq, *J* = 6, 7 Hz, HC-4'), 2.01-1.95 (2H, m, H_2C-6''), 1.92 (1H, dq, *J* = 14, 7.5 Hz, HC-1''''), 1.90 (3H, s, H_3C-1''), 1.81 (1H, dq, *J* = 14, 7.5 Hz, HC-1''''), 1.65 (3H, s, H_3CC-4''), 1.48 (3H, d, *J* = 7 Hz, H_3C-5'), 1.38 (3H, s, H_3CC-2), 1.31 (3H, d, *J* = 7 Hz, H_3C-1'), 1.26 (3H, s, H_3C-2), 0.98 (3H, t, *J* = 7.5 Hz, H_3C-2''''), 0.90 (3H, t, *J* = 7.5 Hz, H_3C-7''), 0.78 (3H, d, *J* = 6.5 Hz, H_3CC-5 [NOE on irradiation of HC-2']).

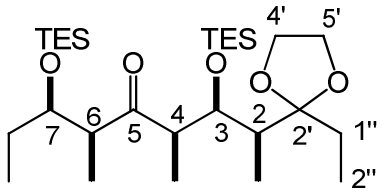
^{13}C NMR (125 MHz, C_6D_6) δ 134.2 (d, C-3'), 134.0 (s, C-2' or C-4'), 133.3 (d, C-5'), 132.3 (s, C-2' or C-4'), 114.8 (s, C-2'''), 99.2 (s, C-2), 83.8 (d, C-6), 82.1 (d, C-4), 70.1 (d,

C-3'), 65.8 (t, C-4'''), 65.5 (t, C-5'''), 44.3 (d, C-4'), 38.3 (d, C-2'), 34.0 (d, C-5), 30.9 (q, CH_3C-2), 27.0 (t, C-1''''), 22.3 (t, C-6''), 19.8 (q, CH_3C-2), 17.4 (q, CH_3C-4''), 14.9 (q, C-7''), 13.7 (q, C-1''), 13.2 (q, C-1'), 12.9 (q, CH_3C-5), 12.7 (q, C-5'), 7.9 (q, C-2'''').

LRMS (ESI), *m/z* (relative intensity): 447 ($[M+23]^+$, 100), 367 (1), 269 (1), 228 (2), 186 (10), 112 (11), 101 (31).

HRMS (ESI), *m/z* calcd for $C_{25}H_{44}O_5$+Na: 447.3080 ; found: 447.3091.

(2S,3R,4R,6S,7R)-2-(2-Ethyl-1,3-dioxolan-2-yl)-4,6-dimethyl-3,7-bis[(triethylsilyl)oxy]nonan-5-one (175).



175

TES-Cl (1.40 mL, 1.27 g, 8.43 mmol) and imidazole (0.62 g, 9.0 mmol) were added sequentially to a stirred solution of (+)-**165** (2.50 g, 6.45 mmol) in DMF (20 mL) at ambient temperature under argon. After 18 h, the mixture was diluted by ethyl acetate, washed with 1 M aq HCl, dried over Na_2SO_4, concentrated, and fractionated by FCC (10% ethyl acetate in hexane) to give the titled compound (2.84 g, 83%): $[\alpha]_D$ +16 (*c* 0.5, $CHCl_3$).

IR (DRIFT) ν_{max}: 1704 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.26 (1H, dd, *J* = 4.5, 4.5 Hz, HC-3), 3.95-3.86 (4H, m, H_2C-4', H_2C-5'), 3.82 (1H, ddd, *J* = 5, 5.5, 6 Hz, HC-7), 2.95 (1H, dq, *J* = 4.5, 7 Hz, HC-

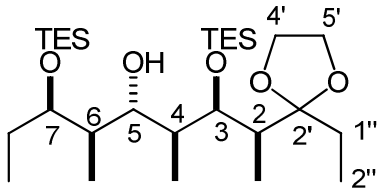
4), 2.85 (1H, dq, *J* = 6, 7 Hz, HC-6), 1.83 (1H, dq, *J* = 4.5, 7 Hz, HC-2), 1.69 (1H, dq, *J* = 14.5, 7.5 Hz, HC-1''), 1.58 (1H, dq, *J* = 14.5, 7.5 Hz, HC-1''), 1.49 (1H, ddq, *J* = 4.5, 14.5, 7.5 Hz, HC-8), 1.32 (1H, ddq, *J* = 4.5, 14.5, 7.5 Hz, HC-8), 1.12 (3H, d, *J* = 7 Hz, H_3CC-4), 1.07 (3H, d, *J* = 7 Hz, H_3CC-6), 0.96 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.95 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.90 (3H, d, *J* = 7 Hz, H_3C-1), 0.88 (3H, t, *J* = 7.5 Hz, H_3C-9), 0.84 (3H, t, *J* = 7.5 Hz, H_3C-2''), 0.65-0.59 (12H, m, H_2CSi ×6).

^{13}C NMR (125 MHz, $CDCl_3$) δ 216.0 (s, C-5), 113.8 (s, C-2'), 74.8 (d, C-7), 71.1 (d, C-3), 65.2 (t ×2, C-4', C-5'), 52.4 (d, C-4), 49.7 (d, C-6), 43.1 (d, C-2), 28.0 (t, C-8), 27.2 (t, C-1''), 13.5 (q, CH_3C-6), 12.4 (q, CH_3C-4), 11.2 (q, C-1), 9.7 (q, C-9), 7.5 (q, C-2''), 7.4 (q ×3, CH_3CSi), 7.2 (q ×3, CH_3CSi), 5.6 (t ×3, CH_2Si), 5.4 (t ×3, CH_2Si).

LRMS (CI, NH_3), *m/z* (relative intensity): 531 ($[M+1]^+$, 0.4), 501 (1), 399 (12), 337 (7), 273 (5), 173 (32), 132 (31), 101 (100).

HRMS (CI, NH_3), *m/z* calcd for $C_{28}H_{58}O_5Si_2$+H: 531.3901; found: 531.3897.

(2S,3R,4S,5S,6R,7R)-2-(2-Ethyl-1,3-dioxolan-2-yl)-4,6-dimethyl-3,7-bis((triethylsilyl)oxy)nonan-5-ol (176).



176

$LiHBEt_3$ (1 M in THF; 1.5 mL, 1.5 mmol) was added dropwise via syringe to a pre-cooled, stirred solution of **175** (270 mg, 0.51 mmol) in THF (24 mL) at 0 °C under

argon. The reaction mixture was removed from the ice bath and allowed to slowly warm to ambient temperature. After 18 h, the reaction mixture was cooled to 0 °C and quenched by sequential addition of MeOH (4 mL), phosphate buffer (pH 7; 5 mL), and 30% aqueous H_2O_2 (3 mL) with vigorous stirring. After 20 min, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were washed with H_2O, dried over Na_2SO_4, and concentrated to give crude product whose ^{1}H NMR spectrum indicated the presence of a 7:1 mixture of diastereomers (283 mg). Fractionated crude by FCC (10% ethyl acetate in hexane) gave the titled compound (219 mg, 81%): $[\alpha]_D$ –11 (*c* 1.1, $CHCl_3$).

IR (DRIFT) ν_{max}: 3512 cm^{-1}.

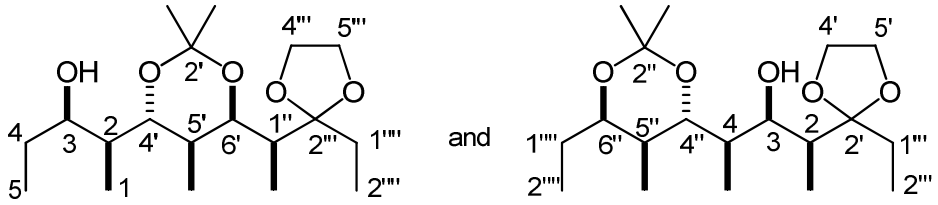
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.30 (1H, dd, *J* = 1, 6.5 Hz, HC-3), 4.04 (1H, ddd, *J* = 1.5, 5.5, 9.5 Hz, HC-7), 3.95-3.86 (4H, m, H_2C-4', H_2C-5'), 3.48 (1H, ap d, *J* = 8.5 Hz, HO), 3.29 (1H, ddd, *J* = 3.5, 8.5, 9.5 Hz, HC-5), 1.93 (1H, dq, *J* = 6.5, 7 Hz, HC-2), 1.88 (1H, ddq, *J* = 1, 9.5, 7 Hz, HC-4), 1.79-1.67 (2H, m, HC-1", HC-6), 1.66-1.54 (3H, m, HC-1", H_2C-8), 1.04 (3H, d, *J* = 7 Hz, H_3CC-6), 0.98 (3H, d, *J* = 7 Hz, H_3C-1), 0.96 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.95 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.84 (3H, t, *J* = 7.5 Hz, H_3C-2"), 0.81 (3H, t, *J* = 7.5 Hz, H_3C-9), 0.71 (3H, d, *J* = 7 Hz, H_3CC-4), 0.65 (6H, ap q, *J* = 8 Hz, H_2CSi ×3), 0.62 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 114.2 (s, C-2'), 77.5 (s, C-5), 75.1 (d, C-7), 71.5 (d, C-3), 65.3 (t, C-4'), 65.1 (t, C-5'), 43.8 (d, C-4), 43.5 (d, C-2), 34.2 (d, C-6), 28.0 (t, C-8), 27.1 (t, C-1"), 13.1 (q, C-1), 11.1 (q, CH_3C-6), 10.2 (q, C-9), 9.9 (q, CH_3C-4), 7.6 (q, C-2"), 7.4 (q ×3, CH_3CSi), 7.1 (q ×3, CH_3CSI), 5.8 (t ×3, CH_2Si), 5.7 (t ×3, CH_2Si).

LRMS (CI, NH_3), *m/z* (relative intensity): 533 ($[M+1]^+$, 1), 401 (6), 373 (7), 339 (39), 201 (11), 173 (12), 132 (31), 132 (11), 101 (100).

HRMS (CI, NH_3), *m/z* calcd for $C_{28}H_{60}O_5Si_2$+H: 533.4058 ; found: 533.4032.

(2*S*,3*R*)-2-[(4*S*,5*S*,6*R*)-6-((*S*)-1-(2-Ethyl-1,3-dioxolan-2-yl)ethyl]-2,2,5-trimethyl-1,3-dioxan-4-yl)pentan-3-ol (177) and (2*S*,3*R*,4*R*)-2-(2-Ethyl-1,3-dioxolan-2-yl)-4-[(4*R*,5*S*,6*R*)-6-ethyl-2,2,5-trimethyl-1,3-dioxan-4-yl]pentan-3-ol (178).



177 **178**

p-TsOH·H_2O (2.5 mg, 0.01 mmol) was added to a stirred solution of **182** (10 mg, 0.033 mmol) in CH_2Cl_2 (1 mL) and 2,2-dimethoxypropane (0.5 mL). After 5 min, the mixture was diluted with CH_2Cl_2, washed with saturated aq $NaHCO_3$, dried over Na_2SO_4, concentrated, and fractionated by PTLC (20% ethyl acetate in hexane) to give an inseparable 7:3 mixture of **177** and **178**, respectively (8 mg, 70%).

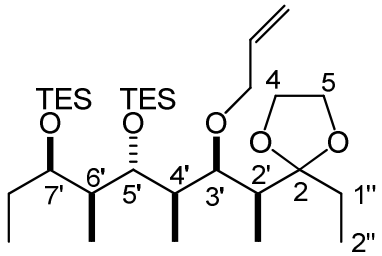
^{1}H NMR (500 MHz, C_6D_6) δ (* major isomer) 4.31 (0.7H, ddd, *J* = 1, 3.5, 5 Hz, *HC-3), 4.08 (0.3H, dd, *J* = 4.5, 7.5 Hz, HC-6'), 4.05-4.01 (0.3H, m, HC-3), 3.73 (0.7H, ddd, *J* = 4.5, 4.5, 9 Hz, *HC-6" [$^3J_{HC\text{-}5"}$ = 4.5 Hz]), 3.48 (4H, br s, *H_2C-C-4', H_2C-4''', *H_2C-5', H_2C-5'''), 3.36 (1H, ap dd, *J* = 4, 8 Hz, *HC-4", HC-4'), 3.24 (0.7H, d, *J* = 1 Hz, *HOC-3), 3.11 (0.3H, d, *J* = 2 Hz, HOC-3), 2.17 (0.7H, dq, *J* = 5, 7 Hz, *HC-2), 2.14-2.04 (1.3H, m, *HC-4, HC-1", HC-5'), 1.91 (0.7H, ddq, *J* = 4.5, 8, 7 Hz, *HC-5" [$^3J_{HC\text{-}6"}$ = 4.5

Hz, $^{3}J_{HC\text{-}4''}$ = 8 Hz]), 1.85 (0.7H, dq, *J* = 14, 7.5 Hz, *HC-1'''), 1.81-1.60 (2H, m, *HC-1''', H_2C-1'''', HC-4), 1.56 (0.3H, ddq, *J* = 2,5, 4, 7 Hz, HC-2), 1.44 (0.7H, ddq, *J* = 9, 13.5, 7.5 Hz, *HC-1''''), 1.39 (2.1H, d, *J* = 7 Hz, *H_3C-1), 1.37-1.30 (0.3H, m, HC-4), 1.29 (2.1H, s, *H_3C-2''), 1.27 (2.1H, d, *J* = 7 Hz, *H_3C-5), 1.26 (0.9H, s, H_3C-2'), 1.23 (2.1H, s, *H_3C-2''), 1.23 (0.9H, d, *J* = 7 Hz, H_3C-2''), 1.22 (0.9H, s, H_3C-2'), 1.15 (0.7H, ddq, *J* = 4.5, 13.5, 7.5 Hz, *HC-1''''), 1.06 (0.9H, t, *J* = 7 Hz, H_3C-5), 1.06 (0.9H, d, *J* = 7 Hz, HC-2), 0.98 (2.1H, t, *J* = 7.5 Hz, *H_3C-2'''), 0.97 (0.9H, d, *J* = 7 Hz, H_3CC-5'), 0.93 (0.9H, t, *J* = 7.5 Hz, H_3C-2''''), 0.88 (2.1H, t, *J* = 7.5 Hz, *H_3C-2''''), 0.81 (2.1H, d, *J* = 7 Hz, *H_3CC-5'').

^{13}C NMR (125 MHz, $CDCl_3$) δ (* major isomer) 114.4* (s), 113.8 (s), 101.2 (s), 100.9* (s), 81.0 (d), 80.2* (d), 73.7 (d), 71.5* (d), 70.8* (d), 69.3 (d), 65.3 (t), 65.23* (t), 65.21* (t), 65.0 (t), 42.4* (d), 40.0* (d), 39.8 (d), 39.2 (d), 39.0 (d), 37.0* (d), 27.4 (t), 26.78* (t), 26.73 (t), 25.4* (q, CH_3C-2''), 25.3 (q, CH_3C-2'), 23.8* (t), 23.7* (q, CH_3C-2''), 23.6 (q, CH_3C-2'), 13.6 (q), 12.4 (q), 12.34* (q), 12.29* (q), 12.0 (q), 11.2 (q), 10.8* (q ×2), 7.6* (q), 7.4 (q).

HRMS (ESI), *m/z* calcd for $C_{19}H_{36}O_5$+Na: 367.2454; found: 367.2443.

2-[(2*S*,3*R*,4*S*,5*S*,6*S*,7*R*)-3-Allyloxy-4,6-dimethyl-5,7-bis[(triethylsilyl)oxy]nonan-2-yl]-2-ethyl-1,3-dioxolane (180).



180

KHMDS (0.5 M in toluene; 1.3 mL, 0.65 mmol) was added dropwise via syringe to a stirred solution of **176** (170 mg, 0.32 mmol) in THF (10 mL) at −78 °C under argon. After 5 min, allyl bromide (140 μL, 193 mg, 1.59 mmol) was added. The reaction was allowed to warm to ambient temperature and after 18 h, was quenched by addition of MeOH (2 mL). The mixture was diluted with CH_2Cl_2, washed with saturated aq NH_4Cl, dried over Na_2SO_4, concentrated, and fractionated by FCC (10% ethyl acetate in hexane) to give the titled compound (168 mg, 92%): $[\alpha]_D$ –21 (*c* 1.1, $CHCl_3$).

IR (DRIFT) ν_{max}: 3080, 1642 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93-5.85 (1H, ap ddt, *J* = 10.5, 17, 5 Hz, HC=), 5.23 (1H, ap dddd, *J* = 1.5, 1.5, 2, 17 Hz, HC=), 5.06 (1H, dddd, *J* = 1.5, 1.5, 2, 10.5 Hz, HC=), 4.09 (1H, dddd, *J* = 1.5, 1.5, 5, 13 Hz, H_2CO), 3.98 (1H, dddd, *J* = 1.5, 1.5, 5, 13 Hz, H_2CO), 3.95-3.88 (4H, m, H_2C-4, H_2C-5), 3.81-3.77 (2H, m, HC-3', HC-7'), 3.66 (1H, dd, *J* = 4, 6 Hz, HC-5'), 1.87-1.78 (2H, m, HC-2', HC-4'), 1.75-1.67 (3H, m, H_2C-1'', HC-6'), 1.62-1.49 (2H, m, H_2C-8'), 1.00 (3H, d, *J* = 7 Hz, H_3C-1'), 0.965 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.96 (3H, d, *J* = 7 Hz, $H_3CC'4'$), 0.955 (9H, t, *J* = 8 Hz, H_3CCSi ×3), 0.87

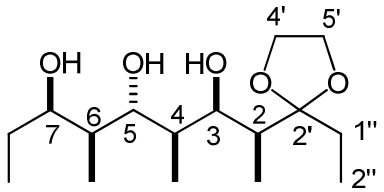
(3H, d, J = 7 Hz, H_3CC-6'), 0.86 (3H, t, J = 7.5 Hz, H_3C-2''), 0.85 (3H, t, J = 7.5 Hz, H_3C-9'), 0.69-0.55 (6H, m, H_2CSi ×6).

^{13}C NMR (125 MHz, $CDCl_3$) δ 136.0 (d, CH=), 115.2 (s, C-9), 114.1 (t, CH_2=), 77.6 (d, C-3'??), 76.2 (d, C-5), 74.7 (d, C-7), 72.5 (t, CH_2OAll), 65.7 (t, C-4), 65.0 (t, C-5), 44.6 (d, C-2'), 43.5 (d, C-4'), 42.4 (d, C-6'), 28.3 (t, C-8'), 27.2 (t, C-1''), 12.8 (q, CH_3C-4'), 10.5 (q, CH_3C-6'), 10.1 (q, CH_3C-1'), 9.7 (q, C-9'), 7.45 (q, C-2''), 7.36 (q ×3, CH_3CSi), 7.33 (q ×3, CH_3CSi), 6.0 (t ×3, CH_2Si), 5.8 (t ×3, CH_2Si).

LRMS (CI, NH_3), *m/z* (relative intensity): 573 ($[M+1]^+$, 7), 311 (11), 247 (21), 173 (22), 132 (35), 101 (100).

HRMS (CI, NH_3), *m/z* calcd for $C_{31}H_{64}O_5Si_2$+H: 573.4371; found: 573.4373.

(2S,3R,4S,5S,6S,7R)-2-(2-Ethyl-1,3-dioxolan-2-yl)-4,6-dimethylnonane-3,5,7-triol (182).



182

TBAF (110 mg, 0.42 mmol) was added to a stirred solution of **176** (200 mg, 0.40 mmol) in THF (5 mL) at ambient temperature. After 2 h, the mixture was diluted with CH_2Cl_2, washed with saturated aq NH_4Cl, dried over Na_2SO_4, concentrated, and fractionated by FCC (40% ether in CH_2Cl_2) to give the titled compound (88 mg, 77%): $[\alpha]_D$ –13 (*c* 0.1, $CHCl_3$).

IR (DRIFT) ν_{max}: 3431 cm^{-1}.

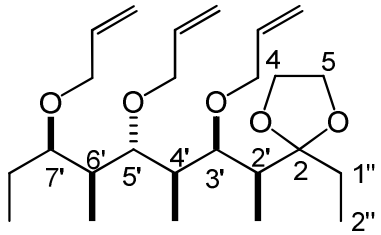
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.48 (1H, br s, HOC-5), 4.23 (1H, br s, HC-3), 4.01-3.94 (4H, m, H_2C-4', H_2C-5'), 3.83 (1H, br dd, *J* = 5.5, 7 Hz, HC-7), 3.68 (1H, br dd, *J* = 7, 8 Hz, HC-5), 3.48 (1H, br s, HOC-7), 2.98 (1H, br s, HOC-3), 2.06 (1H, ddq, *J* = 3.5, 7, 7 Hz, HC-4), 2.02 (1H, dq, *J* = 1.5, 7 Hz, HC-2), 1.82 (1H, ddq, *J* = 1.5, 6, 7 Hz, HC-6), 1.73-1.60 (2H, m, H_2C-1''), 1.56 (1H, ddq, *J* = 7, 13,5, 7.5 Hz, HC-8), 1.42 (1H, ddq, *J* = 5.5, 13.5, 7.5 Hz, HC-8), 1.08 (3H, d, *J* = 7 Hz, H_3C-1), 0.97 (3H, d, *J* = 7 Hz, H_3CC-6), 0.96 (3H, t, *J* = 7.5 Hz, H_3C-9), 0.93 (3H, d, *J* = 7 Hz, H_3CC-4), 0.89 (3H, t, *J* = 7.5 Hz, H_3C-2'').

^{13}C NMR (125 MHz, $CDCl_3$) δ 115.1 (s, C-2'), 80.6 (d, C-5), 74.2 (d, C-7), 72.1 (d, C-3), 65.4 (t, C-4'), 65.1 (t, C-5'), 40.0 (d, C-2), 39.6 (d, C-4), 38.3 (d, C-6), 27.1 (t, C-1'' or C-8), 27.0 (t, C-1'' or C-8), 13.2 (q, CH_3C-4), 11.8 (q, CH_3C-6), 11.0 (q, C-9), 10.1 (q, C-1), 8.1 (q, C-2'').

LRMS (CI, NH_3), *m/z* (relative intensity): 305 ($[M+1]^+$, 6), 243 (38), 225 (44), 101 (100).

HRMS (CI, NH_3), *m/z* calcd for $C_{16}H_{32}O_5$+H: 305.2328; found: 533.2325.

2-[(2S,3R,4S,5S,6S,7R)-3,5,7-Tris(allyloxy)-4,6-dimethylnonan-2-yl]-2-ethyl-1,3-dioxolane (187).



187

A solution of **182** (93 mg, 3.06 mmol) in THF (20 mL) was added dropwise via syringe to a stirred suspension of KH (oil free; 0.52 g, 13 mmol) and DMPU (1.6 mL, 1.7 g, 13 mmol) in THF (100 mL) at 0 °C. After 10 min, allyl bromide (1.7 mL, 2.4 g, 19 mmol) was added dropwise via syringe. The reaction mixture was allowed to warm to ambient temperature and after18 h, was cooled down to 0 °C and quenched by slow addition of MeOH (6 mL) (Caution: H_2 evolution). The mixture was diluted with CH_2Cl_2, washed sequentially with saturated aq NH_4Cl and brine, dried over Na_2SO_4, and fractionated by FCC (10% ethyl acetate in hexane) to give the titled compound (1.18 g, 91%): $[\alpha]_D$ –25 (*c* 1.0, $CHCl_3$).

IR (DRIFT) ν_{max}: 3088, 1646 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95-5.86 (3H, m, HC= ×3), 5.25 (3H, br d, *J* = 17 Hz, HC= ×3), 5.11-5.06 (3H, m, HC= ×3), 4.09-4.01 (5H, m, H_2CO-allyl ×2.5), 3.96-3.88 (5H, m, H_2C-4, H_2C-5, H_2CO-allyl ×0.5), 3.76 (1H, dd, *J* = 3, 4.5 Hz, HC-3'), 3.50 (1H, ddd, *J* = 3, 6, 7 Hz, HC-7'), 3.21 (1H, dd, *J* = 5, 7 Hz, HC-5'), 1.91 (1H, ddq, *J* = 4.5, 5, 7 Hz, HC-4'), 1.87 (1H, dq, *J* = 3, 7 Hz, HC-2'), 1.81 (1H, ddq, *J* = 3, 7, 7 Hz, HC-6'), 1.76,

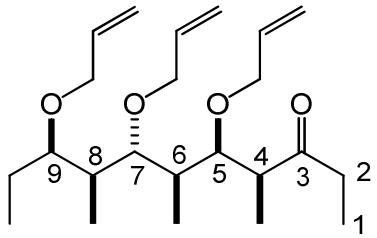
1.63 (3H, m, H_2C-1'', HC-8'), 1.46 (1H, ddq, *J* = 7, 14, 7.5 Hz, HC-8'), 1.01 (3, d, *J* = 7 Hz, H_3C-1'), 0.99 (3, d, *J* = 7 Hz, H_3CC-4'), 0.94 (3, d, *J* = 7 Hz, H_3CC-6'), 0.89 (3, t, *J* = 7.5 Hz, H_3C-9'), 0.86 (3, t, *J* = 7.5 Hz, H_3C-2'').

^{13}C NMR (125 MHz, $CDCl_3$) δ 136.1 (d, CH=), 136.0 (d, CH=), 135.9 (d, CH=), 115.9 (t, CH_2=), 115.5 (t, CH_2=), 115.3 (t, CH_2=), 114.2 (s, C-2), 84.2 (d, C-5'), 80.5 (d, C-7'), 77.3 (d, C-3'), 72.8 (t, CH_2O), 72.4 (t, CH_2O), 71.0 (t, CH_2O), 65.6 (t, C-4), 65.1 (t, C-5), 44.6 (d, C-2'), 41.8 (d, C-4'), 38.6 (d, C-6'), 27.2 (t, C-1''), 25.0 (t, C-8'), 12.8 (q, CH_3C-4'), 11.3 (q, CH_3C-6'), 10.4 (q, C-9'), 10.1 (q, C-1'), 7.5 (q, C-2'').

LRMS (CI, NH_3), *m/z* (relative intensity): 425 ($[M+1]^+$, 5), 367 (4), 237 (26), 141 (3), 101 (100), 99 (12), 57 (4).

HRMS (CI, NH_3), *m/z* calcd for $C_{25}H_{44}O_5$+H: 425.3267; found: 425.3259.

(4*S*,5*R*,6*S*,7*S*,8*S*,9*R*)-5,7,9-Tris(allyloxy)-4,6,8-trimethylundecan-3-one (188).



188

$FeCl_3 \cdot 6H_2O$ (150 mg, 0.55 mmol) was added to a stirred solution of **187** (603 mg, 1.42 mmol) in THF (8.5 mL) and CH_2Cl_2 (8.5 mL). After 19 h, the reaction mixture was diluted with CH_2Cl_2, washed sequentially with H_2O and brine, dried over Na_2SO_4, and concentrated to give the titled compound (538 mg, quantitative) that was homogeneous by TLC and ^{1}H NMR: $[\alpha]_D$ –4 (*c* 2.2, $CHCl_3$).

IR (DRIFT) ν_{max}: 3087, 1711, 1646 cm^{-1}.

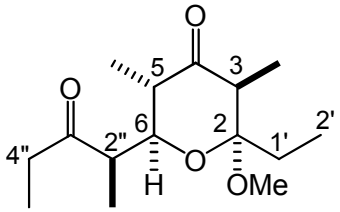
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93-5.83 (3H, m, HC= ×3), 5.26-5.21 (3H, m, HC= ×3), 5.10-5.07 (3H, m, HC= ×3), 4.12-3.96 (5H, m, H_2CO ×2.5), 3.86 (1H, dddd, *J* = 1.5, 1.5, 5, 12.5 Hz, H_2CO ×0.5), 3.76 (1H, dd, *J* = 3, 6.5 Hz, HC-5), 3.50 (1H, ddd, *J* = 3, 5.5, 8 Hz, HC-9), 3.16 (1H, dd, *J* = 4, 7.5 Hz, HC-7), 2.84 (1H, dq, *J* = 7, 7 Hz, HC-4), 2.53 (1H, dq, *J* = 18, 7.5 Hz, HC-2), 2.46 (!H, dq, *J* = 18, 7.5 Hz, HC-2), 1.76 (1H, ddq, *J* = 3, 7, 7 Hz, HC-8), 1.73-1.63 (2H, m, HC-6, HC-10), 1.44 (1H, ddq, *J* = 8, 14, 7.5 Hz, HC-10), 1.13 (3H, d, *J* = 7 Hz, H_3CC-4), 1.02 (3H, t, *J* = 7 Hz, H_3C-1), 1.00 (3H, d, *J* = 7 Hz, H_3CC-6), 0.87 (3H, t, *J* = 7.5 Hz, H_3C-11), 0.86 (3H, d, *J* = 7 Hz, H_3CC-8).

^{13}C NMR (125 MHz, $CDCl_3$) δ 214.3 (s, C-3), 136.0 (d, CH=), 135.8 (d, CH=), 135.5 (d, CH=), 116.1 (t, CH_2=), 115.7 (t, CH_2=), 115.5 (t, CH_2=), 85.0 (d, C-7), 80.3 (d, C-9), 80.0 (d, C-5), 73.3 (t, CH_2O), 72.8 (t, CH_2O), 70.8 (t, CH_2O), 50.2 (d, C-4), 38.9 (d, C-6 or C-8), 38.8 (d, C-6 or C-8), 35.8 (t, C-2), 24.7 (t, C-10), 13.6 (q, CH_3C-6), 13.1 (q, CH_3C-4), 11.0 (q, CH_3C-8), 10.5 (q, C-11), 7.9 (q, C-1).

LRMS (CI, NH_3), *m/z* (relative intensity): 381 ($[M+1]^+$, 100), 323 (39), 265 (33), 237 (34), 195 (47), 155 (17), 101 (18), 99 (32), 57 (10).

HRMS (CI, NH_3), *m/z* calcd for $C_{23}H_{40}O_4$+H: 381.3005; found: 381.2997.

(2*R*,3*S*,5*S*,6*S*)-2-Ethyl-2-methoxy-3,5-dimethyl-6-((*R*)-3-oxopentan-2-yl)dihydro-2*H*-pyran-4(3*H*)-one (189).



189

A solution of **188** (10 mg, 0.026 mmol) in methanol (1.3 mL) was added via syringe to a dry Schlenk flask containing a magnetic stir bar and Ru(IV) catalyst **190** (0.3 mg, 0.6 μmol) under argon. Stirring was initiated and after 10 min, the mixture was diluted with ethyl acetate and washed with distilled water (×3). The organic layer was dried over Na_2SO_4, concentrated to give the crude product (8 mg) whose ^{1}H NMR spectrum indicated a single compound without an allyl group. IBX (15 mg, 0.05 mmol) was added to the solution of the above crude in DMSO (1 mL). After 2 h, the mixture was diluted with ethyl acetate, and washed sequentially with $NaHCO_3$ and brine, dried over Na_2SO_4, concentrated, and fractionated by PTLC (15% ethyl acetate in hexane) to give the titled compound (5.1 mg, 72 %): $[\alpha]_D$ –118 (*c* 0.1, $CHCl_3$).

IR (neat) ν_{max}: 1722, 1703 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.55 (1H, dd, *J* = 3, 10.5 Hz, HC-6), 3.15 (3H, s, H_3CO), 2.77 (1H, dq, *J* = 3, 7 Hz, HC-1''), 2.66 (1H, dq, *J* = 18.5, 7 Hz, HC-4''), 2.63 (1H, dq, *J* = 1, 6.5 Hz, HC-3), 2.55 (1H, dq, *J* = 18.5, 7 Hz, HC-4''), 2.45 (1H, ddq, *J* = 1,10.5, 6.5 Hz, HC-5), 1.95 (1H, dq, *J* = 13.5, 7.5 Hz, HC-1'), 1.56 (1H, dq, *J* = 13.5, 7.5 Hz, HC-1'),

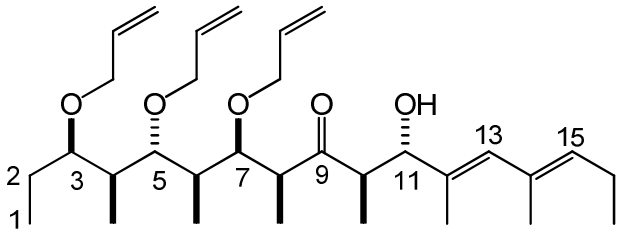
1.34 (3H, d, J = 7 Hz, H_3C-1''), 1.05 (3H, t, J = 7 Hz, H_3C-5''), 1.03 (3H, d, J = 6.5 Hz, H_3CC-5), 0.99 (3H, d, J = 6.5 Hz, H_3CC-3), 0.98 (3H, t, J = 7.5 Hz, H_3C-2').

^{13}C NMR (125 MHz, $CDCl_3$) δ 213.3 (s, C-4 or C-3''), 208.8 (s, C-4 or C-3''), 106.2 (s, C-2), 78.5 (d, C-6), 49.4 (d, C-3), 49.0 (d, C-2''), 47.8 (q, CH_3O), 47.2 (d, C-5), 35.0 (t, C-4''), 26.4 (t, C-1'), 14.4 (q, C-1''), 9.9 (q, C-5''), 8.9 (q, CH_3C-3 or CH_3C-5), 8.4 (q, CH_3C-3 or CH_3C-5), 7.7 (q, C-2').

LRMS (EI), *m/z* (relative intensity): 270 ($[M]^+$, 1), 185 (13), 182 (20), 153 (53), 126 (42), 108 (15), 100 (100), 69 (25), 57 (75).

HRMS (EI), *m/z* calcd for $C_{15}H_{26}O_4$: 270.1831; found: 270.1839.

(3*R*,4*S*,5*S*,6*S*,7*R*,8*S*,10*R*,11*S*,12*E*,14*E*)-3,5,7-Tris(allyloxy)-11-hydroxy-4,6,8,10,12,14-hexamethylheptadeca-12,14-dien-9-one (192).



192

(*c*-Hex)$_2$BCl (1 M in hexane, 1.6 mL, 1.6 mmol), and Et_3N (0.24 mL, 0.17 g, 1.7 mmol) were added sequentially via syringe to a stirred solution of **188** (200 mg, 0.53 mmol) in Et_2O (9 mL) at 0 °C under argon. After 1 h, the reaction mixture was cooled to −78 °C and a solution of the aldehyde **73** (145 mg, 1.05 mmol) in Et_2O (1 mL) was added dropwise via syringe. After 18 h, the reaction was quenched by sequential addition of MeOH (5 mL), phosphate buffer (pH 7; 10 mL), and 30% aqueous H_2O_2 (5 mL) with

vigorous stirring. The reaction vessel was transferred to an ice bath and after 15 min, was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by FCC (10% ethyl acetate in hexane) to give the titled compound: (220 mg, 80%) $[\alpha]_D$ +14 (*c* 0.8, $CHCl_3$).

IR (DRIFT) ν_{max}: 3444, 3087, 1707, 1646 cm^{-1}.

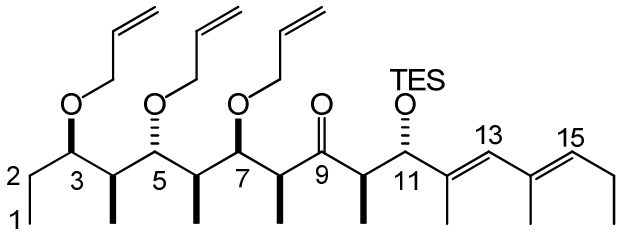
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94-5.86 (3H, m, HC= ×3), 5.84 (1H, br s, HC-13), 5.32 (1H, dd, *J* = 7, 7 Hz, HC-15), 5.28-5.22 (3H, m, HC= ×3), 5.10-5.07 (3H, m, HC= ×3), 4.13-3.99 (6H, m, H_2CO ×2.5, HC-11), 3.91-3.85 (2H, m, H_2CO ×0.5, HC-7), 3.53 (1H, ddd, *J* = 2.5, 5.5, 8 Hz, HC-3), 3.19 (1H, dd, *J* = 4, 7.5 Hz, HC-5), 3.04 (1H, dq, *J* = 7, 7 Hz, HC-8), 2.92 (1H, dq, *J* = 9, 7 Hz, HC-10), 2.14 (1H, d, *J* = 3.5 Hz, HO), 2.09 (2H, ap qn, *J* = 7.5 Hz, H_2C-16), 1.88-1.79 (2H, m, HC-4, HC-6), 1.75 (3H, br s, H_3CC-12), 1.72 (3H, br s, H_3CC-14), 1.72-1.64 (1H, m, HC-2), 1.46 (1H, ddq, *J* = 8, 14, 7.5 Hz, HC-2), 1.18 (3H, d, *J* = 7 Hz, H_3CC-8), 1.06 (3H, d, *J* = 7 Hz, H_3CC-6), 0.99 (3H, t, *J* = 7.5 Hz, H_3C-17), 0.93 (3H, d, *J* = 7 Hz, H_3CC-10), 0.89 (3H, d, *J* = 7 Hz, H_3CC-4), 0.89 (3H, t, *J* = 7.5 Hz, H_3C-1).

^{13}C NMR (125 MHz, $CDCl_3$) δ 217.8 (s, C-9), 136.1 (d, CH=), 135.9 (d, CH=), 135.7 (d, CH=), 133.8 (s, C-12 or C-14), 133.2 (d ×2, C-13, C-15), 131.5 (s, C-12 or C-14), 116.0 (t, CH_2=), 115.8 (t, CH_2=), 115.5 (t, CH_2=), 85.1 (d, C-5), 81.2 (d, C-11), 80.4 (d, C-3), 79.2 (d, C-7), 73.4 (t, CH_2O), 73.0 (t, CH_2O), 70.8 (t, CH_2O), 50.8 (d, C-8), 49.0 (d, C-10), 39.4 (d, C-6), 38.9 (d, C-4), 24.7 (t, C-2), 21.6 (t, C-16), 16.9 (q, CH_3C-14), 14.8 (q, CH_3C-10), 14.3 (q, C-17), 13.8 (q, CH_3C-6), 12.8 (q, CH_3C-8), 12.6 (q, CH_3C-12), 11.0 (q, CH_3C-4), 10.5 (q, C-1).

LRMS (CI, NH_3), *m/z* (relative intensity): 536 ($[M+18]^+$, 1), 519 ($[M+1]^+$, 3), 501 (12), 381 (100), 351 (16), 323 (25), 265 (43), 237 (56), 195 (15), 109 (82).

HRMS (CI, NH_3), *m/z* calcd for $C_{32}H_{54}O_5+NH_4$: 536.4315; found: 536.4335.

(3*R*,4*S*,5*S*,6*S*,7*R*,8*S*,10*R*,11*S*,12*E*,14*E*)-3,5,7-Tris(allyloxy)-4,6,8,10,12,14-hexamethyl-11-(triethylsilyloxy)heptadeca-12,14-dien-9-one (193a).



193a

TESOTf (26 µl, 30 mg, 0.11 mmol) and 2,6-lutidine (22 µl, 20 mg, 0.19 mmol) were added sequentially to a stirred solution of **192** (50 mg, 0.096 mmol) in CH_2Cl_2 (1 mL). After 1 h, the mixture was diluted with CH_2Cl_2, washed with saturated aq $NaHCO_3$, dried over Na_2SO_4, concentrated, and fractionated by FCC (10% ethyl acetate in hexane) to give the titled compound (53 mg, 87%).

IR (DRIFT) ν_{max}: 3080, 1709, 1647 cm^{-1}.

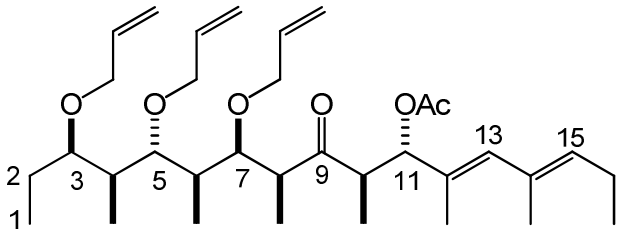
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95-5.83 (3H, m, HC= ×3), 5.77 (1H, br s, HC-13), 5.29-5.21 (4H, m, HC= ×3, HC-15), 5.10-5.06 (3H, m, HC= ×3), 4.15 (1H, d, *J* = 9.5 Hz, HC-11), 4.08-4.01 (5H, m, H_2CO ×2, HC-7), 3.97 (1H, dddd, *J* = 1.5, 1.5, 5.5, 12.5 Hz, H_2CO ×0.5), 3.89 (1H, dddd, *J* = 1.5, 1.5, 5.5, 12.5 Hz, H_2CO ×0.5), 3.50 (1H, ddd, *J* = 3, 5.5, 7.5 Hz, HC-3), 3.2 (1H, dd, *J* = 5, 7 Hz, HC-5), 3.03 (1H, dq, *J* = 7, 9.5 Hz, HC-10), 2.73

(1H, dq, J = 5, 7 Hz, HC-8), 2.09 (2H, ap dq, J = 7, 7.5 Hz, H_2C-16), 1.89-1.80 (2H, m, HC-4, HC-6), 1.71 (3H, s, H_3CC-14), 1.70 (3H, d, J = 1 Hz, H_3CC-12), 1.70-1.62 (1H, m, HC-2), 1.46 (1H, ddq, J = 7, 14, 7.5 Hz, HC-2), 1.26 (3H, d, J = 7 Hz, H_3CC-8), 1.03 (3H, d, J = 7 Hz, H_3CC-4), 0.99 (3H, t, J = 7.5 Hz, H_3C-17), 0.95 (3H, d, J = 7 Hz, H_3CC-4), 0.88 (9H, t, J = 8 Hz, H_3CCSi ×3), 0.88 (3H, t, J = 7.5 Hz, H_3CC-1), 0.81 (3H, d, J = 7 Hz, H_3CC-10), 0.51 (6H, ap q, J = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 216.3 (s, C-9), 136.1 (d, CH=), 135.9 (d, CH=), 135.7 (d, CH=), 134.6 (s, C-12 or C-14), 132.9 (d, C-13), 132.6 (d, C-15), 131.5 (s, C-12 or C-14), 115.7 (t ×2, CH_2=), 115.5 (t, CH_2=), 84.6 (d, C-5), 82.5 (d, C-11), 80.4 (d, C-3), 78.3 (d, C-7), 73.1 (t, CH_2O), 73.0 (t, CH_2O), 70.9 (t, CH_2O), 52.0 (d, C-8), 47.4 (d, C-10), 40.1 (d, C-6), 38.8 (d, C-4), 24.9 (t, C-2), 21.6 (t, C-16), 16.8 (q, CH_3C-14), 15.1 (q, CH_3C-10), 14.3 (q, C-17), 13.4 (q, CH_3C-6), 12.4 (q, CH_3C-12), 11.8 (q, CH_3C-8), 11.4 (q, CH_3C-4), 10.4 (q, CH_3C-1), 7.1 (q ×3, CH_3CSi), 5.0 (t ×3, CH_2Si).

HRMS (ESI), *m/z* calcd for $C_{38}H_{68}O_5Si$+Na: 655.4728; found: 655.4740.

(3*R*,4*S*,5*S*,6*S*,7*R*,8*S*,10*R*,11*S*,12*E*,14*E*)-3,5,7-Tris(allyloxy)-4,6,8,10,12,14-hexamethyl-9-oxoheptadeca-12,14-dien-11-yl Acetate (193b).



193b

Ac_2O (100 μL, 108 mg, 1.05 mmol), $^{i}Pr_2EtN$ (0.27 mL, 0.20 g, 1.6 mmol), and DMAP (10 mg, 0.08 mmol) were added sequentially to a stirred solution of **192** (136 mg, 0.262 mmol) in CH_2Cl_2 (8 mL). After 18 h, the mixture was diluted with CH_2Cl_2, washed with saturated aq $NaHCO_3$, dried over Na_2SO_4, concentrated, and fractionated by PTLC (10% ethyl acetate in hexane) to give the titled compound (146 mg, quantitative): $[\alpha]_D$ +4 (*c* 1.3, $CHCl_3$).

IR (DRIFT) ν_{max}: 3086, 1745, 1711 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.99 (1H, br s, HC-5), 5.94-5.84 (3H, m, HC= ×3), 5.33 (1H, br dd, *J* = 7, 7 Hz, HC-3), 5.28-5.21 (4H, m, HC= ×3, HC-11), 5.11-5.08 (3H, m, HC= ×3), 4.14-3.96 (5H, m, H_2CO ×2.5), 3.87 (1H, dddd, *J* = 1.5, 1.5, 5, 12.5 Hz, H_2CO ×0.5), 3.84 (1H, dd, *J* = 3.5, 6 Hz, HC-7), 3.53 (1H, ddd, *J* = 3, 5.5, 8 Hz, HC-3), 3.19 (1H, dd, *J* = 4, 8 Hz, HC-5), 3.10 (1H, dq, *J* = 10.5, 7 Hz, HC-10), 2.97 (1H, dq, *J* = 6, 7 Hz, HC-8), 2.11-2.03 (2H, m, H_2C-16), 1.91 (3H, s, H_3CCO), 1.84 (1H, ddq, *J* = 3, 8, 7 Hz, HC-4), 1.71 (1H, ddq, *J* = 3.5, 4, 7 Hz, HC-6), 1.74-1.64 (1H, m, HC-2), 1.72 (6H, s, H_3CC-12, H_3CC-14), 1.46 (1H, ddq, *J* = 8, 14, 7.5 Hz, HC-2), 1.19 (3H, d, *J* = 7 Hz, H_3CC-8), 1.07 (3H, d, *J* = 7 Hz, H_3CC-6), 0.97 (3H, t, *J* = 7.5 Hz, H_3C-17), 0.96 (3H, d, *J* = 7 Hz, H_3CC-10), 0.88 (3H, t, *J* = 7.5 Hz, H_3C-1), 0.87 (3H, d, *J* = 7 Hz, H_3CC-4).

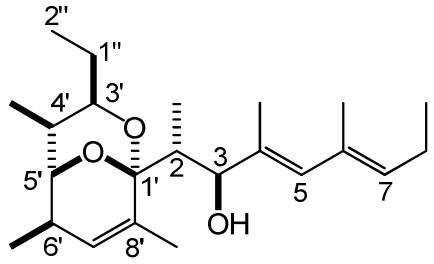
^{13}C NMR (125 MHz, $CDCl_3$) δ 214.3 (s, C-9), 169.5 (s, O=CO), 136.0 (d, CH=), 135.8 (d, CH=), 135.7 (d, C-13), 135.5 (d, CH=), 133.8 (d, C-3), 131.4 (s, C-12 or C-14), 129.6 (s, C-12 or C-14), 116.0 (t, CH_2=), 115.7 (t, CH_2=), 115.6 (t, CH_2=), 85.0 (d, C-5), 82.0 (d, C-11), 80.4 (d, C-3), 79.0 (d, C-7), 73.4 (t, CH_2O), 72.9 (t, CH_2O), 70.7 (t, CH_2O), 50.3 (d, C-8), 46.8 (d, C-10), 39.5 (d, C-6), 38.8 (d, C-4), 24.5 (t, C-2), 21.6 (t, C-16),

21.4 (q, CH_3CO), 16.8 (q, CH_3C-14), 14.7 (q, CH_3C-10), 14.2 (q, C-17), 13.9 (q, CH_3C-6), 13.3 (q, CH_3C-12), 12.6 (q, CH_3C-8), 10.9 (q, CH_3C-4), 10.5 (q, C-1).

LRMS (CI, NH_3), *m/z* (relative intensity): 578 ($[M+18]^+$, 17), 561 ($[M+1]^+$, 3), 535 (18), 501 (27), 443 (22), 351 (55), 295 (15), 237 (100), 99 (58).

HRMS (CI, NH_3), *m/z* calcd for $C_{34}H_{56}O_6+NH_4$: 578.4415; found: 578.4408.

(2*R*,3*S*,4*E*,6*E*)-2-((1*R*,3*R*,4*S*,5*R*,6*R*)-3-Ethyl-4,6,8-trimethyl-2,9-dioxabicyclo[3.3.1]non-7-en-1-yl)-4,6-dimethylnona-4,6-dien-3-ol (194a).



194a

A solution of **193a** (11 mg, 0.017 mmol, 0.02M) in methanol (8 mL) was added via syringe to a dry Schlenk flask containing Ru(IV) catalyst **190** (0.4 mg, 0.8 µmol) under argon. The reaction mixture was kept at 30 °C. After 20 min, the reaction mixture was diluted with ethyl acetate, washed sequentially with distilled water and brine, dried over Na_2SO_4, concentrated, and fractionated by PTLC (40 % ethyl acetate in hexane) to give the titled compound (5 mg, 79%).

IR (DRIFT) ν_{max}: 3479 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 (1H, br s, HC-5), 5.76 (1H, br d, *J* = 5 Hz, HC-7 '), 5.31 (1H, br t, *J* = 7 Hz, HC-7), 5.06 (1H, br s, HO), 4.44 (1H, d, *J* = 9 Hz, HC-3), 3.95

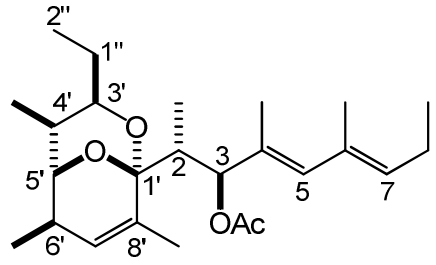
(1H, ddd, *J* = 3, 5.5, 8 Hz, HC-3'), 3.67 (1H, br s, HC-5'), 2.11-2.02 (3H, m, HC-2, H_2C-8), 1.98 (, br dq, *J* = 5, 7 Hz, HC-6'), 1.77 (3H, s, H_3CC-4), 1.72 (3H, s, H_3CC-6), 1.61 (3H, s, H_3CC-8'), 1.53 (1H, ddq, *J* = 8, 13, 7.5 Hz, HC-1''), 1.41-1.31 (2H, m, HC-1'', HC-4'), 1.15 (3H, d, *J* = 7 Hz, H_3CC-4'), 1.09 (3H, d, *J* = 7 Hz, H_3CC-6'), 0.98 (3H, t, *J* = 7.5 Hz, H_3C-9), 0.86 (3H, t, *J* = 7.5 Hz, H_3C-2''), 0.65 (3H, d, *J* = 7 Hz, H_3C-1).

^{13}C NMR (125 MHz, $CDCl_3$) δ 135.0 (s, C-4), 132.6 (d, C-5), 132.02 (d, C-7), 131.93 (s, C-6), 131.1 (d, C-7'), 129.9 (s, C-8'), 101.3 (s, C-9'), 79.94 (d, C-3 or C-5'), 79.86 (d, C-3 or C-5'), 72.1 (d, C-3'), 40.5 (d, C-2), 36.6 (d, C-4'), 34.7 (d, C-6'), 25.7 (t, C-1''), 21.6 (t, C-8), 20.6 (q, CH_3C-6'), 18.2 (q, CH_3C-8'), 17.0 (q, CH_3C-6), 14.4 (q, C-9), 13.1 (q, CH_3C-4'), 12.5 (q, CH_3C-4), 12.2 (q, C-1), 10.0 (q, C-2'').

LRMS (EI), *m/z* (relative intensity): 362 ([M]$^+$, 4), 224 (37), 139 (35), 137 (100), 122 (10), 109 (24), 69 (14), 57 (16).

HRMS (EI), *m/z* calcd for $C_{23}H_{38}O_3$: 362.2821; found: 362.2825.

(2*R*,3*S*,4*E*,6*E*)-2-((1*R*,3*R*,4*S*,5*R*,6*R*)-3-Ethyl-4,6,8-trimethyl-2,9-dioxabicyclo[3.3.1]non-7-en-1-yl)-4,6-dimethylnona-4,6-dien-3-yl Acetate (194b).



194b

A solution of **193b** (12 mg, 0.021 mmol) in methanol (10 mL) was added via syringe to a dry Schlenk flask containing Ru(IV) catalyst **190** (0.3 mg, 0.6 μmol) under argon. The reaction mixture was kept at 30 °C. After 20 min, the reaction mixture was diluted with ethyl acetate, washed sequentially with distilled water and brine, dried over Na_2SO_4, concentrated, and fractionated by PTLC (40 % ethyl acetate in hexane) to give the titled compound (6.2 mg, 72%): $[\alpha]_D$ –52 (*c* 0.1, $CHCl_3$).

IR (DRIFT) ν_{max}: 1737 cm^{-1}.

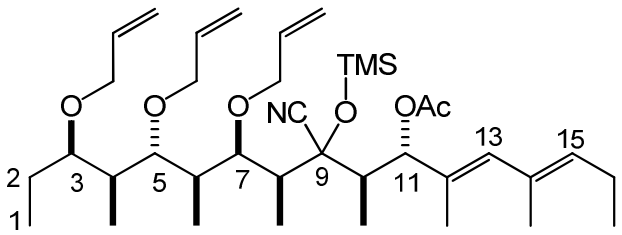
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.98 (1H, s, HC-5), 5.74 (1H, d, *J* = 8.5 Hz, HC-3), 5.72 (1H, dq, *J* = 5, 1.5 Hz, HC-7'), 5.33 (1H, br dd, *J* = 7, 7 Hz, HC-7), 3.78 (1H, ddd, *J* = 3, 5.5, 8 Hz, HC-3'), 3.61 (1H, br s, HC-5'), 2.25 (1H, dq, *J* = 8.5, 7 Hz, HC-2), 2.07 (2H, ap dq, *J* = 7, 7.5 Hz, H_2C-8), 1.97 (3H, s, H_3CCO), 1.95-1.90 (1H, m, HC-6'), 1.75 (3H, d, *J* = 1 Hz, H_3CC-4), 1.72 (3H, br s, H_3CC-6), 1.59 (3H, dd, *J* = 1.5, 1.5 Hz, H_3CC-8'), 1.45-1.36 (1H, ddq, *J* = 8, 13, 7.5 Hz, HC-1''), 1.30-1.21 (2H, m, HC-1'', HC-4'), 1.08 (3H, d, *J* = 7 Hz, H_3CC-4'), 1.05 (3H, d, *J* = 7 Hz, H_3CC-6'), 0.97 (3H, t, *J* = 7.5 Hz, H_3C-9), 0.82 (3H, t, *J* = 7.5 Hz, H_3C-2''), 0.7 (3H, d, *J* = 7 Hz, H_3C-1).

^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9 (s, CO), 133.8 (d, C-5), 133.0 (d, C-7), 131.9 (s, C-4 or C-6), 131.7 (s, C-4 or C-6), 130.9 (d, C-7'), 130.4 (s, C-8'), 99.5 (s, C-9'), 80.0 (d, C-5'), 79.5 (d, C-3), 71.2 (d, C-3'), 39.5 (d, C-2), 36.7 (d, C-4'), 35.0 (d, C-6'), 25.6 (t, C-1''), 21.9 (q, CH_3CO), 21.6 (t, C-8), 20.6 (q, CH_3C-6'), 18.5 (q, CH_3C-8'), 16.9 (q, CCH_3C-6), 14.3 (q, C-9), 13.8 (q, CCH_3C-4), 13.3 (q, CH_3C-4'), 12.1 (q, C-1), 10.1 (q, C-2'').

LRMS (EI), *m/z* (relative intensity): 404 ($[M]^+$, 9), 344 (23), 228 (13), 207 (14), 149 (28), 137 (100), 121 (60), 109 (33), 93 (16), 69 (29).

HRMS (EI), *m/z* calcd for $C_{25}H_{40}O_4$: 404.2927; found: 404.2918.

(3*R*,4*S*,5*S*,6*S*,7*R*,8*S*,10*R*,11*S*,12*E*,14*E*)-3,5,7-Tris(allyloxy)-9-cyano-4,6,8,10,12,14-hexamethyl-9-((trimethylsilyl)oxy)heptadeca-12,14-dien-11-yl Acetate (196).



196

The solid complex KCN·18-crown-6 (87 mg, 0.26 mmol) was added to a stirred solution of **193b** (96 mg, 0.171 mmol) in TMSCN (1 mL) at ambient temperature under argon. After 12 h, the solvent was removed under vacuum and the residue was fractionated by FCC to give the titled compound as a ca. 1.4:1 mixture of diastereomers (95 mg, 84%).

IR (DRIFT) ν_{max}: 3079, 1743, 1646 cm^{-1}.

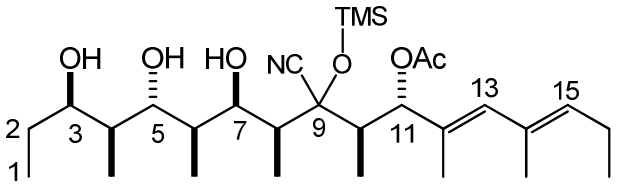
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.03-5.86 (4H, m, HC= ×3, HC-13), 5.33-5.22 (4H, m, HC= 3, HC-15), 5.14-5.06 (4H, m, HC= ×3, HC-11), 4.26-3.85 (6.6H, m, H_2C ×3, HC-7 ×0.6), 3.77 (0.4H, br dd, *J* = 3, 3 Hz, HC-7), 3.46 (0.6H, ddd, *J* = 4, 5.5, 7 Hz, HC-3), 3.36 (0.4H, ddd, *J* = 4, 6, 7 Hz, HC-3), 3.22 (1H, ap t, *J* = 6 Hz, HC-5), 2.50 (0.6H, dq, *J* = 9.5, 7 Hz, HC-10), 2.43 (0.4H, dq, *J* = 9.5, 7 Hz, HC-10), 2.12-2.00 (3H, m, HC-8, H_2C-16), 2.08 (1H, s, H_3CCO), 2.02 (2H, s, H_3CCO), 1.90-1.75 (2H, m, HC-4, HC-6), 1.72 (s) and 1.71 (s) (6H, s, H_3C-12, H_3C-14), 1.71-1.41 (2H, m, H_2C-2), 1.19 (1H, d, *J* = 7 Hz, H_3CC-8), 1.15 (2H, d, *J* = 7 Hz, H_3CC-8), 1.02 (2H, d, *J* = 7 Hz, H_3C-10), 1.01-

0.86 (9H, m, CH_3 ×3), 0.72 (1H, d, H_3C-10), 0.31 (5.4H, s, *J* = 7 Hz, H_3CSi ×3), 0.28 (3.6H, s, H_3CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ (* major isomer) 170.5* (s, C=O), 169.6 (s, C=O), 135.9 (d, CH=), 135.83 (d, CH=), 135.77 (d, CH=), 135.7 (d ×2, CH=), 135.5 (d, CH=), 135.2* (d) and 133.8* (d), 135.1 (d) and 133.6 (d), 131.3 (s) and 130.7 (s), 131.2* (s) and 130.6* (s), 120.9* (s, CN), 120.8 (s, CN), 116.1 (t ×2, CH_2=), 115.9 (t ×2, CH_2=), 115.6 (t, CH_2=), 115.4 (t, CH_2=), 84.42* (d, C-5), 84.37 (d, C-5), 80.7 (d, C-3 or C-11), 80.64* (d, C-11), 80.56 (d, C-3 or C-11), 80.5* (d, C-3), 77.35* (s, C-9; confirmed by DEPT), 76.2 (d, C-7), 75.8* (d, C-7), 73.4 (t, CH_2O), 73.2* (t, CH_2O), 73.1 (t, CH_2O), 72.4* (t, CH_2O), 71.0 (t, CH_2O), 70.6* (t, CH_2O), 47.3 (d, C-8), 46.4* (d, C-8), 42.6 (d, C-4), 42.2* (d ×2, C-4, C-10), 40.5 (d, C-10), 38.63 (d, C-6), 38.56* (d, C-6), 25.1 (t, C-2), 24.7* (t, C-2), 21.7 (q, CH_3CO), 21.62* (t ×2, C-16), 21.57* (q, CH_3CO), 16.7* (q ×2, CH_3C-14), 14.2* (q ×2, C-17), 13.6 (q, CH_3C-12), 13.4* (q, CH_3C-10), 13.3* (q, CH_3C-12), 12.4 (q), 12.0 (q), 11.7* (q), 10.94 (q), 10.89 (q), 10.85 (q), 10.3* (q, C-1), 10.1 (q, C-1), 2.1* (q ×6, CH_3Si).

HRMS (ESI), *m/z* calcd for $C_{38}H_{65}NO_6Si$+Na: 682.4479; found: 682.4486.

(3*R*,4*S*,5*S*,6*S*,7*R*,8*S*,10*R*,11*S*,12*E*,14*E*)-9-Cyano-3,5,7-trihydroxy-4,6,8,10,12,14-hexamethyl-9-((trimethylsilyl)oxy)heptadeca-12,14-dien-11-yl Acetate (197).



197

A solution of **196** (81 mg, 0.12 mmol) in MeOH (4 mL) was added via syringe to a dry Schlenk flask containing a magnetic stir bar and the Ru(IV) catalyst **190** (1.2 mg, 1.1µmol) under argon. The reaction mixture was stirred at 30 °C for 20 min, and then additional Ru(IV) catalyst **190** (1.2 mg, 1.1 µmol) was added. After 20 min, the mixture was diluted with ethyl acetate and washed sequentially with water (×3) and brine, dried over Na_2SO_4, concentrated, and fractionated by FCC (40% ethyl acetate in hexane) to give the titled compound as a 1.1:1 mixture of diastereomers (44 mg, 67%).

IR (DRIFT) ν_{max}: 3439, 1742 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 (0.6H, br s, HC-13), 5.90 (0.4H, br s, HC-13), 5.35-5.31 (1H, m, HC-15), 5.20 (0.4H, d, *J* = 9 Hz, HC-11), 5.11 (0.6H, d, *J* = 9 Hz, HC-11), 4.40 (0.4H, br s, HC-7), 4.33 (0.6H, br s, HC-7), 4.30-4.22 (1H, m, HOC-5), 3.88-3.84 (1H, m, *J* = 7 Hz, HC-3), 3.61-3.57 (1H, m, HC-5), 3.20 (0.4H, br s, HOC-3), 3.07 (0.4H, br s, HOC-7), 2.99 (1.2H, br s, HOC-3, HOC-7), 2.52 (0.4H, dq, *J* = 9, 7 Hz, HC-10), 2.36 (0.6H, dq, *J* = 9, 7 Hz, HC-10), 2.14-2.01 (3H, m, HC-8, H_2C-16), 2.07 (1.8H, s, H_3CCO), 2.03 (1.2H, s, H_3CCO), 1.94-1.76 (2H, m, HC-4, HC-6), 1.73-1.71 (6H, m, H_3CC-12, H_3CC-14), 1.60-1.50 (1H, m, HC-2), 1.49-1.38 (1H, m, HC-2), 1.22 (1.2H, d, *J*

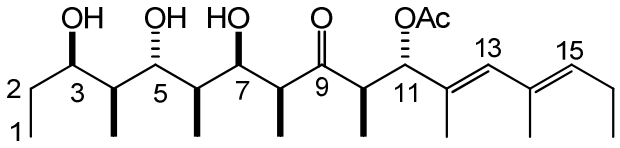
= 7 Hz, H_3CC-8), 1.16 (1.8H, d, *J* = 7 Hz, H_3CC-8), 1.08 (1.2H, d, H_3CC-8), 1.00-0.92 (10.8H, m, H_3C ×3.6), 0.89 (1.8H, d, *J* = 7 Hz, H_3CC-10), 0.88 (1.2H, d, *J* = 7 Hz, H_3C ×0.4), 0.31 (9, s, H_3C-Si×3), 0.28 (9, s, H_3C-Si×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ (* major isomer) 170.1* (s, CO), 169.7 (s, CO), 135.45* (d, C-13), 135.40 (d, C13), 134.03 (d, C15), 133.95* (d, C-15), 131.19* (s, C-12 or C-14), 131.18 (s, C-12 or C-14), 130.35 (s, C-12 or C-14), 130.33* (s, C-12 or C-14), 121.1 (s, CN), 121.0* (s, CN), 80.8* (d, C-11), 80.5 (d, C-11), 80.2 (d, C-5), 79.9* (d, C-5), 79.6 (s, C-9), 78.9* (s, C-9), 74.5* (d, C-3), 73.8 (d, C-3), 71.2* (d, C-7), 71.0 (d, C-7), 44.8* (d, C-8), 44.1 (d, C-8), 41.4* (d, C-10), 41.3* (d, C-4), 41.2 (d ×2, C-4, C-10), 38.0* (d, C-6), 37.4 (d, C-6), 27.3 (t, C-2), 26.9* (t, C-2), 21.62* (t ×2, C-16), 21.61* (q ×2, CH_3CO), 16.76 (q, CH_3C-14), 16.73* (q, CH_3C-14), 14.2* (q ×3, C-17, CH_3C-10), 13.7* (q, CH_3C-12), 13.6 (q, CH_3C-12), 13.0* (q, CH_3C-10), 12.3 (q), 12.2* (q), 11.7* (q), 11.6 (q), 11.2 (q, CH_3C-8), 10.9* (q), 10.8 (q), 10.1* (q, CH_3C-8), 1.98* (q ×3, CH_3Si), 1.93 (q ×3, CH_3Si).

LRMS (EI), *m/z* (relative intensity): 539 ($[M]^+$, 2), 479 (3), 334 (10), 334 (10), 276 (8), 167 (22), 149 (100), 139 (56), 121 (37), 69 (40).

HRMS (EI), *m/z* calcd for $C_{29}H_{53}NO_6Si$: 539.3642; found: 539.3637.

(3*R*,4*S*,5*S*,6*S*,7*R*,8*S*,10*R*,11*S*,12*E*,14*E*)-3,5,7-Trihydroxy-4,6,8,10,12,14-hexamethyl-9-oxoheptadeca-12,14-dien-11-yl Acetate (198a/b).



198a/b

Pyridine (48 µL, 47 mg, 0.6 mmol), HF·Py (32 µL), and water (2 µL) were added sequentially to a stirred solution of **197** (10.6 mg, 19.6 µmol) in THF (0.6 mL). After 24 h, the reaction mixture was diluted with ethyl acetate and washed sequentially with saturated aq $NaHCO_3$, saturated aq NH_4Cl and brine, dried over Na_2SO_4, and concentrated. The resulting crude product was taken up in a 1:1 (*v*/*v*) mixture of water and MeOH and heated to 60 ºC. After 3 h, the mixture was diluted with CH_2Cl_2 and washed with water. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4, concentrated, and fractionated by PTLC to give the titled compound as a 3:1 mixture of keto and hemiacetal forms, respectively (6.3 mg, 73%).

IR (DRIFT) ν_{max}: 3398, 1743, 1711 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 (0.75H, s, HC-13), 5.90 (0.25H, s, HC-13), 5.33 (0.75H, dd, *J* = 7, 7 Hz, HC-15), 5.32 (0.25H, dd, *J* = 7, 7 Hz, HC-15), 5.19 (0.75H, d, *J* = 10.5 Hz, HC-11), 5.18 (0.25H, d, *J* = 9.5 Hz, HC-11), 4.54 (0.75H, br s, HO), 4.20 (0.75H, br d, *J* = 8.5 Hz, HC-7), 3.91-3.85 (1H, m, OH, HC-3), 3.78 (0.75H, ddd, *J* = 2.5, 6, 7 Hz, HC-3), 3.67-3.62 (1H, m, HC-5), 3.28 (0.25H, dd, *J* = 9.5 Hz, HC-7), 3.06 (0.75H, dq, *J* = 10.5, 7 Hz, HC-10), 2.90 (0.75H, dq, *J* = 8.5, 7 Hz, HC-8), 2.86 (0.75H,

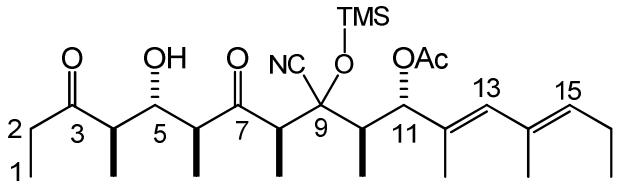
br s, HO), 2.40 (0.25H, br d, *J* = 1 Hz, HO), 2.32 (0.25, dq, *J* = 9.5, 7 Hz, HC-10), 2.10-2.03 (2.75H, m, HC-4, H_2C-16), 2.03 (0.75H, s, H_3CCO), 1.93 (2.25H, s, H_3CCO), 1.85-1.80 (0.25H, m, HC-4), 1.74-1.66 (6.75H, m, H_3CC-12, H_3CC-14, HC-8), 1.65-1.57 (0.75H, s, HC-2, HC-4, HC-6), 1.54-1.47 (1.5H, s, H_2C-2), 1.39-1.32 (0.25H, m, HC-2), 1.27 (2.25H, d, *J* = 7 Hz, H_3C-8), 1.14 (0.75H, d, *J* = 7 Hz, H_3C-4), 1.04 (2.25H, d, *J* = 7 Hz, H_3C-6), 1.02- 0.89 (9.75H, m, H_3C ×3.25), 0.87 (0.75H, d, *J* = 7 Hz, H_3CC-10), 0.83 (2.25H, d, *J* = 7 Hz, H_3CC-4).

^{13}C NMR (125 MHz, $CDCl_3$) δ (* major isomer) 216.0* (s, C-9), 169.8 (s, COO), 169.5* (s, COO), 135.9* (d, C-13), 135.1 (d, C-13), 134.0* (d, C-15), 133.7 (d, C-15), 131.3* (s, C-12 or C-14), 130.6 (s, C-12 or C-14), 129.1* (s ×2, C-12 or C-14), 100.9 (s, C-9), 82.8* (d, C-11), 81.7 (d, C-11), 80.1* (d, C-5), 78.9 (d, C-5), 76.9* (d, C-3), 75.8 (d, C-7), 71.34* (d, C-7), 71.26 (d, C-3), 50.8* (d, C-8), 47.5* (d, C-10), 44.1 (d), 42.4 (d, C-10), 40.6 (d), 39.4* (d, C-4), 36.3* (d, C-6), 35.4 (d), 27.7 (t, C-2), 25.2* (t, C-2), 21.64* (t ×2, C-16), 21.61 (q, CH_3CO), 21.3* (q, CH_3CO), 16.77* (q, CH_3C-14), 16.75 (q, CH_3C-14), 14.9* (q, CH_3C-10), 14..4 (q), 14.3* (q, CH_3C-8 or C-17), 14.2* (q, CH_3C-8 or C-17), 13.5 (q ×2), 13.2* (q, CH_3C-12), 13.0 (q), 12.4 (q), 12.3* (q, CH_3C-4 or CH_3C-6), 12.0* (q, CH_3C-4 or CH_3C-6), 11.3 (q), 11.2* (q, C-1), 11.1 (q), 10.8 (q).

LRMS (EI), *m/z* (relative intensity): 422 ($[M-18]^+$, 0.5), 362 (4), 235 (10), 195 (17), 149 (62), 138 (68), 121 (121), 109 (46), 69 (42).

HRMS (ESI), *m/z* calcd for $C_{25}H_{44}O_6$+Na: 463.3030; found: 463.3043.

(4*R*,5*S*,6*S*,8*R*,10*R*,11*S*,12*E*,14*E*)-9-Cyano-5-hydroxy-4,6,8,10,12,14-hexamethyl-3,5-dioxo-9-((trimethylsilyl)oxy)heptadeca-12,14-dien-11-yl Acetate (200).



200

Oxalyl chloride (140 µL, 201 mg, 1.6 mmol) was added to a stirred solution of DMSO (0.23 mL, 25 mg, 3.2 mmol) in CH_2Cl_2 (1 mL) at −78 °C under argon. After 30 min, a solution of **197** (44 mg, 0.08 mmol) in CH_2Cl_2 (0.4 ml) was added dropwise via syringe to the above Swern reagent. After 2 h, Et_3N (0.66 mL, 480 mg, 4.7 mmol) was added to the reaction mixture. After 30 min, the reaction mixture was transferred to a −50 °C bath. After 30 min, the mixture was diluted with ethyl acetate, washed with saturated aq $NaHCO_3$ solution (×2), dried over Na_2SO_4, concentrated, and fractionated by PTLC (40% ethyl acetate in hexane) to give the titled compound as a 1.2:1 mixture of diastereomers (27.5 mg, 63%).

colorless oil, TLC R_f = 0.5 (40% ethyl acetate in hexane).

IR (DRIFT) ν_{max} 3472, 1741, 1717, 1702 cm^{-1}.

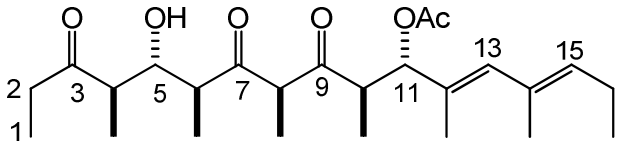
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 (1H, s, HC-13), 5.35-5.29 (1H, m, HC-15), 5.14 (0.5H, d, *J* = 9 Hz, HC-11), 5.07 (0.5H, d, *J* = 10 Hz, HC-11), 3.71 (0.5H, ddd, *J* = 5, 7, 7 Hz, HC-5), 3.66 (10.5H, ddd, *J* = 3, 8.5, 9.5 Hz, HC-5), 3.60 (0.5H, d, *J* = 9.5 Hz, OH), 3.43 (0.5H, q, *J* = 7 Hz, HC-8), 3.25 (0.5H, d, *J* = 7 Hz, OH), 3.17 (0.5H, q, *J* = 7 Hz, HC-8), 2.89-2.80 (1H, m, HC-4 or HC-6), 2.78-2.67 (1H, m, HC-4 or HC-6), 2.66-2.55

(1H, m, HC-2), 2.53 (0.5H, dq, *J* = 10, 7 Hz, HC-10), 2.51-2.40 (1H, m, HC-2), 2.37 (0.5H, dq, *J* = 9, 7 Hz, HC-10), 2.16 (s) and 2.06 (s) (3H, , H_3CCO), 2.10-2.03 (2H, m, H_2C-16), 1.73-1.68 (6H, m, H_3CC-12, H_3CC-14), 1.38 (1.5H, d, *J* = 7 Hz, H_3CC-8), 1.27 (1.5H, d, *J* = 7 Hz, H_3CC-8), 1.26 (1.5H, d, *J* = 7 Hz, H_3CC-4 or H_3CC-6), 1.21 (1.5H, d, *J* = 7 Hz, H_3CC-4 or H_3CC-6), 1.16 (1.5H, d, *J* = 7 Hz, H_3CC-4 or H_3CC-6), 1.08 (1.5H, d, *J* = 7 Hz, H_3CC-10), 1.06 (1.5H, t, *J* = 7 Hz, H_3C-1), 1.04 (1.5H, d, *J* = 7 Hz, H_3CC-4 or H_3CC-6), 1.03 (1.5H, t, *J* = 7 Hz, H_3C-1), 0.98 (1.5H, t, *J* = 7.5 Hz, H_3C-17), 0.97 (1.5H, t, *J* = 7.5 Hz, H_3C-17), 0.80 (1.5H, d, *J* = 7 Hz, H_3CC-10), 0.28 (s) and 0.24 (s) (, , H_3CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 217.8 (s), 216.5 (s), 213.9 (s), 213.7 (s), 170.6 (s), 169.6 (s), 135.5 (d), 135.0 (d), 134.0 (d), 133.6 (d), 131.3 (s), 131.2 (s), 130.8 (s), 130.3 (s), 119.7 (s), 119.4 (s), 80.6 (d), 80.4 (d), 78.1 (d), 77.9 (s), 77.0 (d), 74.7 (s), 55.1 (d), 50.8 (d), 50.3 (d), 49.3 (d), 47.9 (d), 46.1 (d), 41.7 (d), 41.4 (d), 36.4 (t), 35.9 (t), 21.8 (q), 21.63 (t), 21.61 (t), 21.57 (q), 16.8 (q ×2), 15.5 (q), 15.0 (q), 14.9 (q), 14.22 (q), 14.20 (q ×2), 14.16 (q), 13.7 (q), 13.5 (q), 13.4 (q), 12.7 (q), 11.2 (q), 7.7 (q), 7.6 (q), 2.1 (q ×3), 1.8 (q ×3).

HRMS (ESI), *m/z* calcd for $C_{29}H_{53}NO_6Si$+Na: 558.3221; found: 558.3226.

(4*R*,5*S*,6*S*,8*R*,10*R*,11*S*,12*E*,14*E*)-9-cyano-5-hydroxy-4,6,8,10,12,14-hexamethyl-3,5-dioxo-9-((trimethylsilyl)oxy)heptadeca-12,14-dien-11-yl Acetate (202).



202

Pyridine (96 μL, 94 mg, 1.2 mmol), HF·pyridine (70 μL), and water (4 μL) were added sequentially to a solution of **200** (27.5 mg, 51.3 μmol) in THF (1.2 mL). After 24 h, the reaction mixture was diluted with ethyl acetate and washed sequentially with saturated aq $NaHCO_3$, saturated aq NH_4Cl and brine. The organic layer was dried over Na_2SO_4, and concentrated to give the crude product (29.2 mg) as a 1.2:1 mixture cyanohydrin diastereomers. The above crude was taken up in ethyl acetate (1 mL) and silica gel 60 (100 mg) was added. The resulting suspension was stirred for 2 h and then filtered. The combined filtrate and ethyl acetate washings were concentrated to give the titled compound as a mixture of ring-chain and keto-enol tautomers (20.3 mg, 91%).

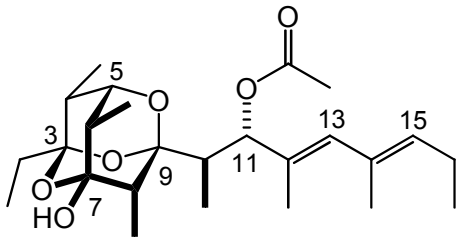
^{1}H NMR (500 MHz, $CDCl_3$) δ (partial data) 16.97 (0.16, s, HO-enol), 6.04-5.89 (1H, several s, HC-13), 5.34 (1H, bt, HC-15), 5.28-5.15 (1H, several d, *J* = 5-6 Hz, HC-11), 4.99 (0.05, s, HO-hemiacetal), 4.04-3.98 (0.7H, q ×2).

^{13}C NMR (125 MHz, $CDCl_3$) δ (partial data) enols: 199.1 (s, CO), 193.6 (s, CO), 105.0 (s, C-8); acetate carbonyls: 169.6 (s, CO), 169.5 (s, CO), 169.35 (s, CO); 82.3 (d, C-11), 82.1 (d, C-11), 81.9 (d, C-11), 61.8 (d, C-8), 59.8 (d, C-8).

LRMS (CI, NH_3), *m/z* (relative intensity): 454 ($[M+18]^+$, 17), 378 (26), 377 (100), 359 (54), 263 (58), 195 (37), 149 (30), 115 (13), 109 (11).

HRMS (CI, NH_3), *m/z* calcd for $C_{25}H_{40}O_6+NH_4$: 454.3169; found: 454.3161.

11-*O*-Acetylmuamvatin (203).



203

Pyridine (48 μL, 47 mg, 0.6 mmol), HF·Py (32 μL), and water (2 μL) was added sequentially to a solution of **202** (10 mg, 23 μmol) in THF (0.6 mL). After 10 days, the reaction mixture was diluted with ethyl acetate and washed sequentially with saturated solution of $NaHCO_3$ (×3), saturated aq NH_4Cl (×3), and brine (5 ml). The organic layer was dried over Na_2SO_4, concentrated, and fractionated by PTLC (40% ethyl acetate in hexane) to give recovered **202** (5.1 mg, 51 %) and the titled compound (4.8 mg, 48%). Resubjecting the recovered **202** to a the same reaction conditions gave **202** (2.4 mg, 24%) and additional titled compound (2.1 mg, 21%): $[\alpha]_D$ +40 (*c* 0.2, $CHCl_3$).

IR (DRIFT) ν_{max}: 3435, 1737 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94 (1H, s, HC-13), 5.53 (1H, d, *J* = 8.5 Hz, HC-11), 5.33 (1H, br dd, *J* = 7, 7.5 Hz, HC-15), 3.80 (1H, br s, HC-5), 2.56 (1H, br s, HO), 2.21 (1H, dq, *J* = 8.5, 7.5 Hz, HC-10), 2.10-2.04 (3H, m, HC-8, H_2C-16), 1.97 (3H, s, H_3CCO), 1.89 (1H, dq, *J* = 1, 7 Hz, HC-6), 1.72 (6H, br s, H_3C-12, H_3C-14), 1.63-1.54 (2H, m, HC-2, HC-4), 1.47 (1H, dq, *J* = 14, 7.5 Hz, HC-2), 1.12 (3H, d, *J* = 7 Hz, H_3CC-

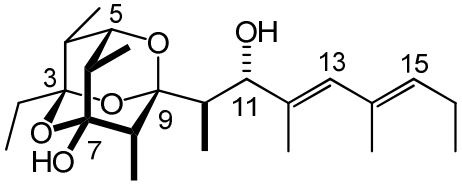
6), 1.09 (3H, d, J = 7 Hz, H_3CC-4), 1.01 (3H, d, J = 6.5 Hz, H_3CC-8), 0.97 (3H, t, J = 7.5 Hz, H_3C-17), 0.93 (3H, t, J = 7.5 Hz, H_3C-1), 0.78 (3H, d, J = 7.5 Hz, H_3CC-10).

^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9 (s, CO), 134.0 (d, C-13), 133.2 (d, C-15), 131.7 (s, C-12 or C-14), 131.6 (s, C-12 or C-14), 103.4 (s, C-9), 102.5 (s, C-3), 97.7 (s, C-7), 79.6 (d, C-11), 78.9 (d, C-5), 43.4 (d, C-6), 39.9 (d, C-10), 38.0 (d, C-4), 35.0 (d, C-8), 30.0 (t, C-2), 21.8 (q, CH_3CO), 21.6 (t, C-16), 16.9 (q, CH_3C-14), 14.3 (q, C-17), 14.0 (q, CH_3C-12), 13.6 (q, CH_3C-4 or CH_3C-6), 13.4 (q, CH_3C-4 or CH_3C-6), 10.5 (q, CH_3C-10), 7.2 (q, CH_3C-8), 6.1 (q, C-1).

LRMS (EI), *m/z* (relative intensity): 436 ($[M]^+$, 4), 419 (3), 376 (10), 195 (29), 176 (20), 153 (18), 149 (100), 139 (50), 121 (87), 57 (55).

HRMS (EI), *m/z* calcd for $C_{25}H_{40}O_6$: 436.2825; found: 436.2816.

Muamvatin (30).



30

DIBAL-H (1 M in toluene; 50 μL, 50 μmol) was added to a stirred solution of **203** (6.8 mg, 15 μmol) in Et_2O (2 mL) at –78 °C under argon. After 2 h, the reaction mixture was diluted with CH_2Cl_2 (20 ml) and washed with aq Rochelle's salt (1.4 M). The aqueous layer was back extracted with CH_2Cl_2. The combined organic layers were

dried over Na_2SO_4, concentrated, and fractionated by PTLC (40% ethyl acetate in hexane) to give the titled compound (5.6 mg, 91%): $[\alpha]_D$ +60 (*c* 0.13, CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (1H, br s, HC-13), 5.31 (1H, br dd, *J* = 7, 7 Hz, HC-15), 4.40 (1H, d, *J* = 9 Hz, HC-11), 4.38 (1H, br s, HOC-11), 3.88 (1H, br s, HC-5), 2.59 (1H, br s, HOC-7), 2.13-2.05 (3H, m, HC-8, H_2C-16), 2.00-1.92 (2H, m, HC-6, HC-10), 1.76 (3H, br s, H_3CC-12), 1.72 (3H, br s, H_3C-14), 1.70-1.65 (2H, m, HC-4, HC-2), 1.59-1.51 (1H, m, HC-2), 1.18 (3H, d, *J* = 7 Hz, H_3CC-4), 1.14 (3H, d, *J* = 7 Hz, H_3CC-6), 1.03 (3H, d, *J* = 7 Hz, H_3CC-8), 0.98 (3H, t, *J* = 7.5 Hz, H_3C-17), 0.95 (3H, t, *J* = 7.5 Hz, H_3C-1), 0.72 (3H, t, *J* = 7 Hz, H_3CC-10).

^{13}C NMR (125 MHz, $CDCl_3$) δ 134.7 (s, C-12), 132.9 (d, C-13), 132.3 (d, C-15), 131.7 (s, C-14), 105.4 (s, C-9), 103.2 (s, C-3), 97.7 (s, C-7), 79.6 (d, C-11), 78.8 (d, C-5), 43.1 (d, C-6), 40.9 (d, C-10), 37.8 (d, C-4), 35.2 (d, C-8), 30.1 (t, C-2), 21.6 (t, C-16), 16.9 (q, CH_3C-14), 14.4 (q, C-17), 13.45 (q, CH_3C-4 or CH_3C-6), 13.41 (q, CH_3C-4 or CH_3C-6), 12.5 (q, CH_3C-12), 10.6 (q, CH_3C-10), 6.9 (q, CH_3C-8), 6.1 (q, C-1).

LRMS (EI), *m/z* (relative intensity): 394 ($[M]^+$, 4), 376 (10), 294 (11), 256 (31), 238 (29), 183 (39), 153 (41), 109 (48), 86 (28), 57 (100).

HRMS (EI), *m/z* calcd for $C_{23}H_{38}O_5$: 394.2719; found: 394.2715.

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